



An Epidemiologic Program for the Study of the Safety and Utilization of LOTRONEX[®] (alosecron HCl) in the U.S.

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Abstract

Background: In November 2002, Lotronex[®] (alosecron HCl) was reintroduced to the U.S. marketplace for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have failed to respond to conventional therapy, whose IBS symptoms are chronic, and who have had other explanatory gastrointestinal medical conditions ruled out. In support of the reintroduction, GSK implemented a comprehensive Risk Management Program (RMP), and several post-marketing study commitments. As part of the post-marketing study commitments, GSK has sponsored parallel claims-based epidemiologic studies in multiple centers to evaluate various elements of the RMP and the safety profile of the product.

Objective: The primary objective of these epidemiologic studies is to address the following research questions:

1. Characterize patients who receive Lotronex
2. Determine how frequently a signed patient-physician agreement (PPA) is in the medical record of a patient prescribed the drug
3. Determine the incidence of events of special interest in all patients who receive Lotronex, those with more than six months of treatment, and those over the age of 65, with appropriate comparison groups
4. Determine risk factors for the events of special interest.

Methods: This is a prospective cohort study, based on the ongoing accrual of data in large, linked health care databases. Data are aggregated across several health plans (n=8.5 million persons) from November 2002 to June 30, 2003. Lotronex users in each data source are being identified, along with a comparison cohort matched on IBS diagnosis, age, gender, health plan, number of gastroenterologist visits, and number and type of dispensings. Both cohorts were defined by baseline diagnosis, procedures and prescriptions.

Results: Between November 2002 and June 2003, we identified 81 Lotronex users with 165 dispensings. Most (90%) were women, and most first prescriptions (75%) were written by gastroenterologists. The investigators retrieved 85% of the records requested to verify compliance with the PPA. Seventy-one percent of the records reviewed contained PPAs signed by both patient and physician. The distribution of diagnoses, procedures, and dispensings were similar for Lotronex users and the comparator cohort.

Conclusion: Results from the first 8 months indicate that far fewer prescriptions have been filled for Lotronex than anticipated. For those dispensings identified, patients and physicians within the participating health plans are completing the PPA as recommended by the U.S. Food and Drug Administration and outlined in the Prescribing Program for Lotronex. Incidence of events of interest will be evaluated as more data are accrued.

Introduction

- Patients with diarrhea-predominant IBS may have chronic or recurrent abdominal pain, irregular bowel movements, and sudden urgent diarrhea.
- Lotronex was initially approved in the U.S. market in February 2000 for women with diarrhea-predominant IBS.
- Due to concerns about safety, Lotronex was voluntarily withdrawn November 1, 2000 by GSK in consultation with the U.S. Food and Drug Administration (FDA).
- In June 2002 the FDA approved the Supplemental New Drug Application for Lotronex under restricted conditions of use. The restrictions included
 - a Risk Management Program (RMP)
 - the Prescribing Program for Lotronex, which is a component of the RMP
 - a revised indication that reflected the intent to reserve Lotronex for patients in whom the medical benefits outweigh the risks: women with severe diarrhea-predominant IBS.

GSK has sponsored parallel claims-based epidemiologic studies in 12 populations to evaluate RMP compliance and quantify the safety profile of the product in real-world clinical practice after the re-introduction.

Objectives

- Evaluate compliance with the RMP:
 - Characterize patients who receive Lotronex, with special attention to apparent contraindications.
 - Determine how frequently a signed PPA is in the medical record of a patient prescribed Lotronex.
- Evaluate safety of Lotronex:
 - Determine the incidence of colon ischemia, bowel motor dysfunction, and gastrointestinal surgery (events of special interest) in all patients who receive Lotronex, those with more than 6 months of treatment, and those over the age of 65, with appropriate comparison groups.
 - Determine risk factors for the events of special interest.

Methods

Data Sources: Table 1 shows the collaborative research team and the associated data sources.

Table 1. Principal Investigators and Database Sources for Claims-Based Observational Studies

Investigator/ Database Source	Comments/Size
Dr. Walker ■ Ingenix Database	The Ingenix Database comprises ~4.2 million insured patients.
Dr. Avorn ■ PA PACE Program ■ New Jersey Medicaid and PAAD Programs	PACE Program: ~221,000 patients over the age of 65. The NJ Program: ~200,000 patients over the age of 65. Of these, approximately 65% are from PAAD, and 35% are from Medicaid.
Dr. Gurwitz ■ Harvard Pilgrim Health Care (~50,000 Medicare paid) ■ Fallon Community Health Plan (Worcester, MA) ■ Group Health Cooperative of Puget Sound (Seattle, WA) ■ Health Partners (Minneapolis, MN) ■ Henry Ford Health Systems (Detroit, MI) ■ Kaiser Permanente Georgia ■ Kaiser Permanente Northwest ■ Kaiser Permanente Colorado (~2,000 Medicare paid) ■ Lovelace Health Systems (Albuquerque, NM)	HMO Research Network Center for Education Research and Therapeutics (CERT) 3.9 million are insured

Study Practices: The data from the Collaborative Research Group are submitted to the RTI-HS Coordinating Center.

The RTI-HS Coordinating Center team

- Performs the quality control checks
- Performs the pooled analysis
- Prepares the report
- Works according to established standard operating procedures and project-specific work practice documents.

Investigator Meetings: The collaborative research team meets approximately every two months to discuss and refine study design and standardize operations as well as other relevant issues.

Methods (continued)

Study Design: This is a claims-based cohort study of Lotronex users and a matched comparator group with IBS.

Study Period: November 2002 through September 30, 2003.

Allosecron Users: All Lotronex users must have at least one pharmacy-dispensing claim for Lotronex.

Non-Lotronex Users Comparator Cohort: A comparator group of patients who were not taking Lotronex were drawn semi-annually. The matching ratio is 4 comparators:1 Lotronex user.

Matching Scheme: A comparator cohort is matched to the patients in the Lotronex users' cohort based on age (five-year age categories), gender, health plan (or site), service for IBS (in the 6 months preceding the index date [Lotronex users—date of first Lotronex dispensing, non-Lotronex users—index date of the matched Lotronex users]), number of GI visits during baseline, and number of dispensings of specific drugs during baseline.

Baseline Period: Up to 6 months preceding and including the index date. Comparator's baseline was fixed to match that of the matched Lotronex user.

Evaluate Compliance with the RMP

- Describe the demographics of patients and indications for Lotronex.
- Determine compliance with PPA by verifying the presence of a PPA signed by both physician and patient in the patient's medical record.

Evaluate Safety of Lotronex

Outcomes Identification: The events of interest are

- Colon ischemia
- Bowel motor dysfunction
- Gastrointestinal surgery.

For safety monitoring, the cumulative data from 12 large health care databases were evaluated every 6 months. Using claims data and algorithms, the Collaborative Research Group identified medical claims related to outcome events of interest.

To validate identified events of interest, a standardized medical record abstraction form was used to abstract medical records.

Safety Review Committee: The medical records were reviewed by an independent Safety Review Committee, which

- Is comprised of three expert clinicians and a consulting statistician.
- Independently reviews all the available clinical documentation and classifies potential cases according to event-specific criteria.
- Is blinded to the exposure status of Lotronex and does not ascertain drug causality for the cases.
- Assigns one of the following to each potential colon ischemia or bowel motor dysfunction event of interest: probable, possible, or unlikely.
- For bowel surgery, determines whether the event took place or not.

IRB Approval

Each investigator site, as well as the RTI-HS Coordinating Center, has undergone a thorough IRB review and approval process specific to their institution.

Results

Evaluate Compliance with the RMP

These results cover the dispensing of Lotronex through September 30, 2003:

- 121 users received a prescription for Lotronex (generally a 30-day supply).
- 277 dispensings were identified.
- 89% of patients were females, and most patients were between the ages of 25 and 64 years (Table 2).

Table 2. Statistics for Lotronex Recipients Pooled Across All Sites

	Total	Male	Female
Total Recipients	121	13	108
Age (years)			
<18	0	0	0
18-34	23	0	23
35-54	65	8	57
55-64	20	4	16
65+	13	1	12

Table 3. Dispensing Rates Pooled Across All Sites

	Lotronex Dispensings	Lotronex Patients	Total Membership	Dispensing Rate (dispensings per 100,000)
Total	277	121	5,882,297	4.71
Region				
Northeast	50	23	1,416,440	3.53
Southeast	111	49	1,408,638	7.88
Midwest	80	33	1,470,332	5.44
West	36	16	1,586,667	2.27

Table 4. Dispensing by Prescribing Physician Specialty Pooled Across All Sites

Prescribing Physician Specialty	First Dispensings		Additional Dispensings	
	#	%	#	%
Gastroenterologist	84	69	100	64
General/ Family Practice	14	12	12	8
Internal Medicine	18	15	26	17
Other	5	5	18	11
Total	121		156	

- 66% of patients received, at most, 2 dispensings.
- 54% of patients were dispensed, at most, 60 tablets.
- We reviewed the available claims data for up to 2 years preceding (average=1.35 years) the index date for possible contraindications.
- Five patients with a history of 5 potential contraindications were found. These were not verified by medical record review.
- 89% (n=91) of the 102 charts sought for review were identified. (At present, some sites were not able to seek out charts).
- 70% (n=64) of the charts contained a PPA signed by the physician and the patient in the patient medical record.

Evaluate Safety of Lotronex—Data Lock Point December 31, 2003

Table 5. Characterization of the Study Cohort

	Lotronex Users N=53		Non-Lotronex Comparator Group N=181	
	#	%	#	%
Total Cohort Size				
Age at start of observation				
<18	0	0.0	5	2.8
18-34	6	10.1	18	10.0
35-54	35	66.1	120	66.3
55-64	9	17.0	30	16.6
65+	3	5.7	8	4.4
Gender				
Male	9	17.0	31	17.1
Female	44	83.0	150	82.9

Results (continued)

Common Diagnoses, Procedures, and Prescriptions in the Baseline Period

- Three of the top four diagnoses (IBS, GI system symptoms, abdominal pain) occurred in both users of Lotronex and comparators preceding the index date.
- Common procedures among both groups reflected routine examinations (office visit, blood work, etc.).
- 9% of users of Lotronex and 18% of the comparators had a dispensing of hyoscyamine sulfate, used for the treatment of IBS. 13% of users of Lotronex and 11% of comparators had dispensings of drugs to treat diarrhea (difenoxylate HCl and dicyclomine HCl).
- Drugs to treat anxiety (e.g., alprazolam) were used by both users of Lotronex (15%) and comparators (12%).
- Drugs for infections (e.g., azithromycin HCl, amoxicillin trihydrate, cephalexin monohydrate) were in the 20 most frequently dispensed drugs in both groups.
- Drugs for constipation-predominant IBS were found among the comparators.

Limitations

- This study represents patients participating in health insurance programs and provides some advantage over a prospective study in that it is not affected by potential patient participation bias.
- The number of users of Lotronex identified in the claims-based observational studies still remains small (n=121).

Research Strategy

As with any collaborative effort across multiple sites, it was important to establish a research strategy to ensure that all the protocols were consistent across sites, and that all groups applied the definitions in the same way.

- The creation of a smaller, working group that met frequently aided in obtaining consensus on detailed, technical questions.
- Slow accumulation of exposures resulted in little data upon which to base study design decisions.

Conclusions

- This study represents an excellent example of collaboration among multiple groups to achieve the implementation of a common protocol and analytic plan.
- There were no notable differences in the distribution of common diagnoses, procedures, and dispensings between the two groups.
- Even though there is often a long lag time to update all documents into a medical record, 70% of the records reviewed had a PPA.

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