Lotronex®(alosetron hydrochloride) Tablets

GlaxoSmithKline

Briefing Document

for the

Drug Safety and Risk Management Committee

May 5, 2004

Table of Contents

Section I: Introduction

Section I: Introduction

Lotronex (alosetron hydrochloride), 1mg BID, was initially approved on February 9, 2000 for the treatment of irritable bowel syndrome (IBS) in women whose predominant bowel symptom was diarrhea. However, post-marketing reports of serious gastrointestinal adverse events led to an evolving and uncertain risk profile that, coupled with the inability of GlaxoSmithKline and FDA to reach a mutually agreed upon risk management program (RMP), led GlaxoSmithKline to voluntarily withdrawal the product from the US market on November 28, 2000.

Subsequent to the withdrawal of Lotronex from the marketplace, the benefit to risk balance of Lotronex was further defined and the significant burden of illness imposed by IBS became better understood. The enhanced understanding of these key drivers for product use facilitated the identification of a new target patient population and development of a RMP. It was agreed that the benefits of treatment with Lotronex outweighed potential risks for women with severe d-IBS who had failed to respond to conventional therapy in a setting where risks could be managed appropriately by the RMP.

On December 7, 2001, GSK submitted a Supplemental New Drug Application (sNDA 21-107/S-005) for Lotronex. This Supplemental Application sought FDA's approval to allow the re-introduction of Lotronex tablets, under modified conditions of use and with restrictions imposed by a RMP. The sNDA contained 19 additional studies in patients with d-IBS for a combined clinical trials database of 11,874 patients who had been treated with alosetron; a substantial body of new efficacy and safety information that was not available for Agency review at the time the product was withdrawn in November 2000. Results from these additional studies demonstrated that alosetron effectively reduced and controlled bowel urgency in patients with severe d-IBD. On June 7, 2002 the sNDA was approved.

The approved indication is the following:

"Because of serious gastrointestinal adverse events, some fatal, reported with use of this drug, LOTRONEX is indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have:

- *chronic IBS symptoms (generally lasting 6 months or longer),*
- *had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and*
- *failed to respond to conventional therapy.*

Diarrhea-predominant IBS is severe if it includes diarrhea and one or more of the following:

- *frequent and severe abdominal pain/discomfort*
- *frequent bowel urgency or fecal incontinence*

- *disability or restriction of daily activities due to IBS.*

Less than 5% of IBS is considered severe.
In men, safety and effectiveness of LOTRONEX have not been established."

The circumstances involved with the withdrawal of the product from the marketplace and the subsequent outcry by patients for the re-introduction of Lotronex led the FDA and GlaxoSmithKline to develop an integrated RMP for Lotronex. The goals of this RMP can be summarized as:

1. Limiting the use of Lotronex to those patients for whom the benefit:risk ratio is most favorable;

2. Providing physicians and patients with information to inform them of and to help them manage the risks associated with the use of Lotronex;

3. Limiting the prescribing of Lotronex to qualified physicians and the appropriate prescribing of Lotronex by these physicians;

4. Providing a framework for ongoing RMP evaluation.

This Briefing Document is being provided in support of the update on the Risk Management Program for Lotronex to the Drug Safety and Risk Management Advisory Committee on May 5, 2004. The Document covers the following topics:

- A description of the following four key components of the RMP for Lotronex;

    1. Enrollment of qualified physicians in a physician prescribing program;

    2. Implementation of a program to educate physicians, pharmacists and patients about the benefits and risks of Lotronex;

    3. Implementation of an enhanced system for collection and reporting of adverse events associated with the use of Lotronex;

    4. Implementation of a plan to evaluate the effectiveness of the RMP for Lotronex;

- A summary of the experience with implementation of the RMP from product reintroduction in November 2002 through January 2004;

- Identification of emerging issues regarding the unintended, yet apparent, impact of the RMP on critical dynamics of product use.

Finally, a number of clinical studies are being conducted as part of our Phase IV commitments. These studies which are not discussed in the Briefing Document because of their ongoing status, are designed to provide additional information on Lotronex and on the disease of irritable bowel syndrome (IBS). Although these are monitored, controlled trials, they do follow the requirements of the RMP with regard to reporting the adverse events of special interest and in informing patients and investigators of the restrictions and risks associated with using Lotronex as specified in the RMP. The following studies are being conducted:

An Open -Label, Parallel-Group, Pharmacokinetics and Tolerability Study of a Single 1mg Oral Dose of Alosetron in Hepatically Impaired Subjects and in Healthy Control Subjects

A Double-blind, Placebo-Controlled, Randomized, Two Way Crossover Study to Evaluated the Potential Inhibition of Alosetron Metabolism by Ketoconazole in Healthy Female Subjects

A Double-blind, Placebo-Controlled, Randomized, Two Way Crossover Study to Evaluated the Potential Inhibition of Alosetron Metabolism by Fluvoxamine in Healthy Female Subjects

A Twelve-Week Randomized Double-Blind, Placebo-Controlled Study with PRN BID and Fixed Dosing of Alosetron in Female Subjects with Severe Diarrhea-Predominant IBS Who Have Failed Conventional Therapy

A Twelve-Week Randomized Double-Blind, Placebo-Controlled Parallel-Group Study To Assess the Safety and Efficacy of 0.5 mg QD and 1 mg BID of Alosetron in Female Subjects with Severe Diarrhea-Predominant IBS Who Have Failed Conventional Therapy

A Case-Historical Control Study to Identify Genetic Markers Associated with Ischemic Colitis and Serious Constipation in Female Subjects Treated with Lotronex

A Clinical Study in Healthy Normal Volunteers to Validate the Methodologies of Laser Doppler Flowmetry (LDF) and Transabdominal Ultrasound Doppler for the Measurement of Colorectal Mucosal Perfusion and Small Intestinal Blood Flow

Pre-clinical Study of the Role of 5-HT3 Receptors in the Regulation of Colonic Muscosal Blood Flow

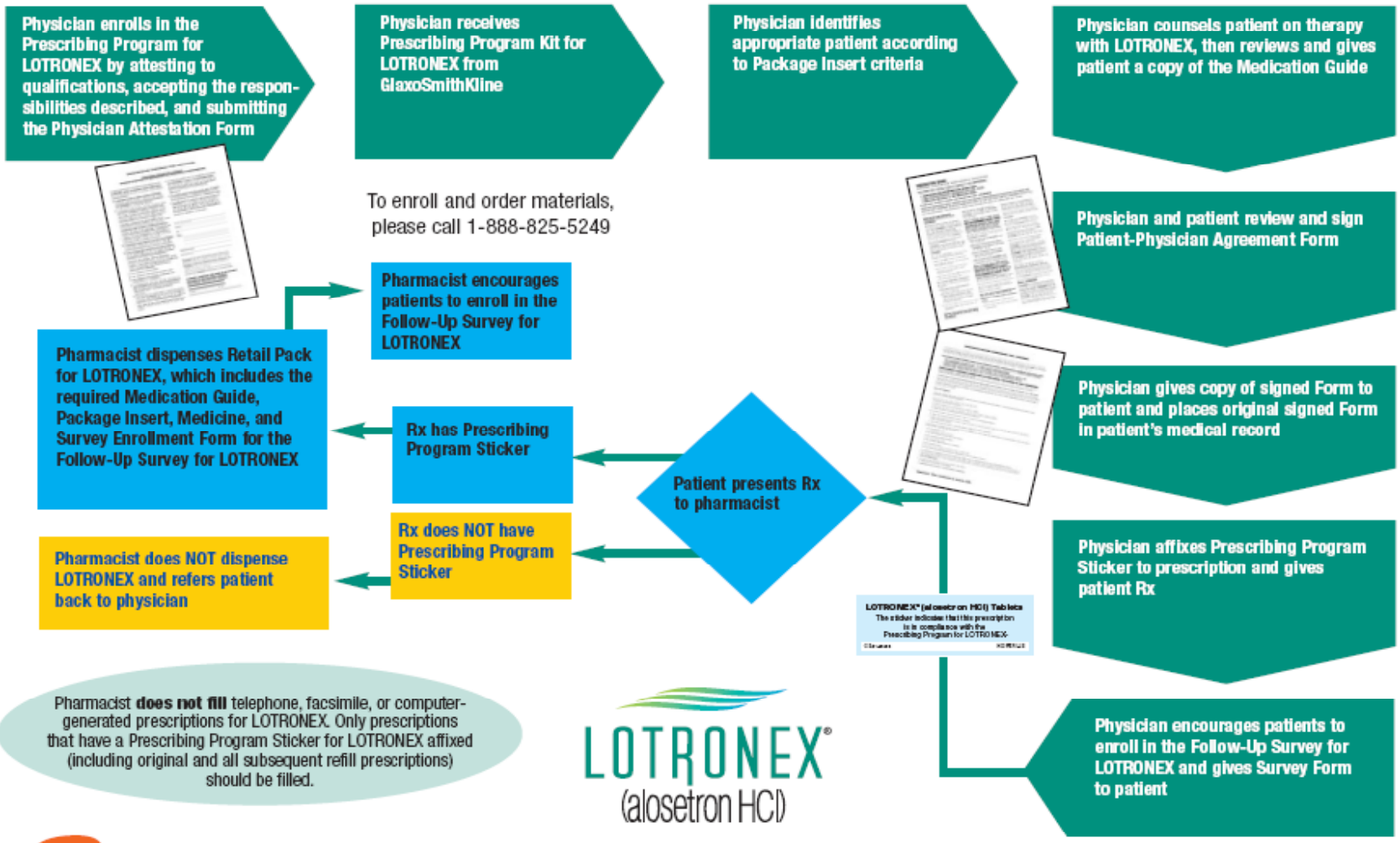
Individual sections of the Briefing Document have been organized to provide a detailed description of each RMP component along with the corresponding data generated since product re-introduction/RMP implementation, where appropriate. A discussion and conclusions, relative to our experience with the RMP for Lotronex, follow the review of emerging issues.

Section II(A): Prescribing Program for Lotronex

Section II(A): Prescribing Program for Lotronex

One of the key elements of the RMP is the Prescribing Program for Lotronex (PPL). Physicians must enroll into this program in order to prescribe Lotronex. Enrollment into the PPL is based on self-attestation of qualifications and acceptance of certain responsibilities in prescribing the medicine. Physicians who are enrolled into the PPL receive Prescribing Program Stickers (i.e., "blue stickers"), that must be affixed to each prescription written for Lotronex. The Prescribing Program Stickers on the prescription alert pharmacists that the prescribing physician is enrolled in the PPL. The PPL is diagrammed in the schematic on the next page of this document.

FLOWCHART: PRESCRIBING PROGRAM FOR LOTRONEX™



GlaxoSmithKline

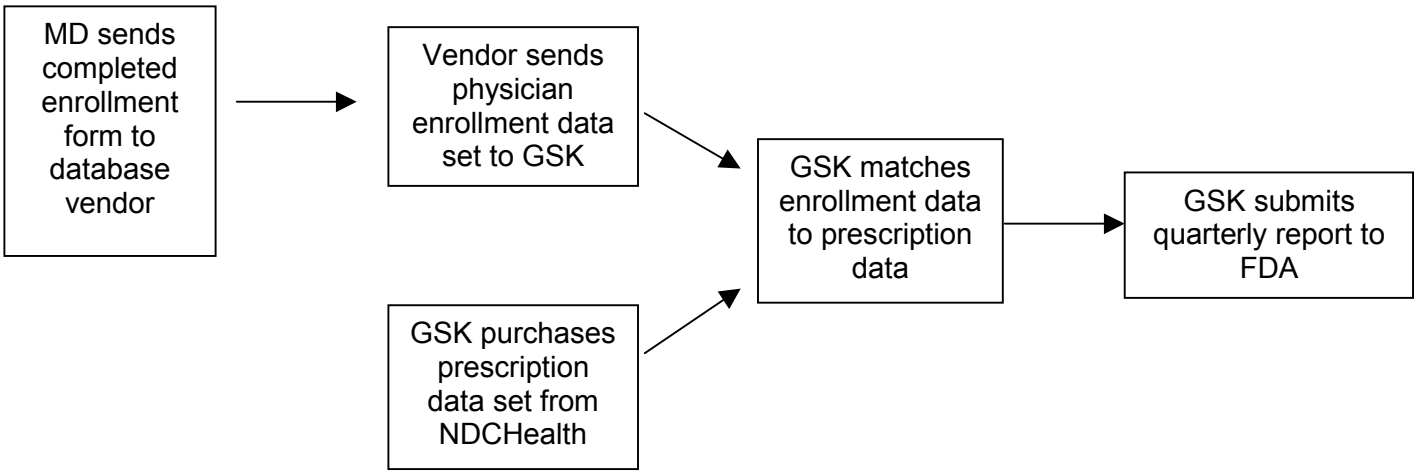
Please consult accompanying important safety and complete Prescribing Information.

A study, entitled*, "A Retrospective Study to Compare the Roster of Physicians Identified in a General Prescription Database as Prescribers of Lotronex® with the Roster of Physicians Enrolled in the Prescribing Program for Lotronex®,"* has been designed to monitor physician prescribing of Lotronex, in fulfillment of a Phase IV commitment.

Methodology and Data Analysis

Data on physician prescriptions were obtained from NDCHealth, which has data on 70% of all retail prescriptions written by all US prescribers. Physicians enrolled in the PPL were compared to NDCHealth list of all physicians within that database who wrote prescriptions for Lotronex. The NDCHealth's data set encompasses 100% of the prescribers and 70% of all retail prescriptions. The data are geographically representative of the US retail market.

The schematic below depicts the process used for analyzing physician prescription data for Lotronex.



The following information has been summarized:

- Number of physicians enrolled in the PPL and the percentage who have prescribed Lotronex;
- Number of non-PPL enrolled physicians in the NDCHealth database who have prescribed Lotronex;
- Geographical and specialty enrollment and prescribing.

Observations: November 2002 - December 2003

Prescribing Program Enrollment

During the period from November 2002 through December 2003, a total of 5,053 physicians enrolled in the PPL. **Table 1** below shows the monthly and cumulative enrollment profiles.

Table 1: PPL Enrollment and Prescribing within the PPL

Month	Number of Physicians Enrolled in PPL	Number Enrolled Prescribing	% of Enrolled Physicians Prescribing
Nov-02	65	4	0%
Dec-02	2.107	204	10%
Jan-03	2,924	535	18%
Feb-03	3,433	691	20%
Mar-03	3,707	803	22%
Apr 03	3,909	869	22%
May 03	4,092	914	22%
Jun 03	4,277	988	23%
Jul 03	4,452	1,017	23%
Aug 03	4,590	1,041	23%
Sep 03	4,728	1,114	24%
Oct 03	4,880	1,120	23%
Nov 03	4,970	1,084	22%
Dec 03	5,053	1,144	23%

Prescribing

For the period November 2002 through December 2003 a total of 30,634 prescriptions have been written by 3,952 physicians. The number of physicians prescribing in each month has risen slightly. This information is displayed in **Table 2**. The average monthly percentage of physicians prescribing while being enrolled in the PPL is approximately 80%. Thus, approximately 20% of the prescribers have not been enrolled in the PPL; however, this "20% group" constantly changes in membership as previously non-enrolled

prescribers either enroll or cease to prescribe and "new" non-enrolled prescribers become a part of this group.

Table 2: Physician Matching to PPL

Month	Number of Physicians Prescribing	Number Enrolled Prescribing	% Physicians Prescribing Enrolled in PPL
Nov-02	10	0	0%
Dec-02	324	204	63%
Jan-03	716	535	75%
Feb-03	888	691	78%
Mar-03	1,015	803	79%
Apr 03	1,061	869	82%
May 03	1,133	914	81%
Jun 03	1,250	988	79%
Jul 03	1,261	1,017	81%
Aug 03	1,273	1,041	82%
Sep 03	1,368	1,114	81%
Oct 03	1,378	1,120	81%
Nov 03	1,305	1,084	83%
Dec 03	1,382	1,144	83%

In each quarter, non-enrolled prescribers have been identified and sent letters and enrollment kits. Overall, this has resulted in approximately 75% of the previously non-enrolled prescribers complying with the program by either enrolling (25%) or ceasing to prescribe (50%).

Medical Specialties

The distribution of physician specialties among enrolled and non-enrolled prescribers is displayed in **Table 3**.

Table 3. Prescribers of Lotronex: Distribution of Physician Specialties (Quarter October 2003-December 2003)

Specialty	Number of Prescribers	Percent of Prescribers Enrolled in the PPL
Gastroenterologists	1,108	92%
Primary Care Physicians*	845	69%
Other**	243	37%
Total	2,196	77%

* GP, family practice, internal medicine

**Most frequent specialties: obstetricians, gynocologists, institutions, general surgery, psychiatry

For the quarter October 2003 through December 2003, the physician specialties most commonly prescribing Lotronex were gastroenterologists (50% of prescribers), and primary care physicians (38%), which is made up of family practitioners and internal medicine physicians and "Other Specialties" 11%. The gastroenterologists have the highest percentage of those prescribing enrolled in the PPL at 92% and the also generate over 60% of the prescriptions. The category "Other Specialties" had the lowest percentage of prescribers not enrolled in the PPL, but prescribing Lotronex; however, they made up the lowest proportion of prescriptions (8%). Included in "Other Specialties" were obstetrics/gynecology, unspecified specialty, general surgery , colon and rectal surgery, and psychiatry.

Because of heterogenous nature of physicians who have prescribed Lotronex and who are not enrolled in the PPL, a targeted mailing program is in place to communicate the requirements of PPL. In addition physician have access to education programs which include information on the PPL.

Geographic Distribution of PPL Participants

Looking across the four regions, the percentage of physicians enrolled in the PPL ranged from 79% in the Midwest region to 75% in the Southeast. Thus, participation in the PPL appears to be equally dispersed across the sections of the country. This information is displayed in **Table 4**.

Table 4: Physician Prescribing Matched to the PPL
(Quarter October 2003-December 2003)

	Number of Physicians Prescribing	Number Enrolled Prescribing	% Physicians Prescribing Enrolled in PPL
Northeast	489	377	77%
Midwest	577	453	79%
Southeast	717	536	75%
West	412	323	78%
Other	1	1	100%
Total	2,196	1,690	77%

Discussion and Conclusions

Overall the Prescribing Program for Lotronex appears to have been effectively implemented. Greater than 80% of the physicians who are prescribing Lotronex are enrolled in the PPL. The majority of the non-enrolled prescribing physicians do respond to the educational communications that stress that only physicians enrolled in the PPL are permitted to prescribe Lotronex. Gastroenterologists make up a majority of the prescribing however there is reasonable participation by primary care physicians which has helped provide access for patients. Overall participation is relatively equal across regions.

While the program has been effectively implemented, it appears to have contributed to limiting patients' access to Lotronex. During the period from November 2002 through December 2003, a total of 5,053 physicians enrolled in the PPL and of that number only 2,532 (50%) wrote at least one prescription for Lotronex. Feedback from physicians from a variety of sources including physician interviews via market research have indicated that physicians are reluctant to participate in the PPL and prescribe Lotronex because of some of the requirements of the RMP.

Section II(B): Educational Programs

Section II(B): Educational Programs

Another element of the RMP for Lotronex has been to develop and implement educational programs for health care professionals in order to facilitate their understanding of the modified conditions of prescribing and the appropriate use of Lotronex. To accomplish this commitment, the following programs have been initiated.

Initial Re-introduction Communications: Letters, Telephone Calls and Sales Representative Activities

With the re-introduction of Lotronex tablets in November 2002, GlaxoSmithKline implemented a broad communication program to provide introductory letters and materials and telephone communications to approximately 500,000 healthcare professionals. In November 2002 a total of 345,000 Dear Doctor letters and 4,500 Dear Healthcare Professional letters for institutions and managed care organizations were mailed. A total of 92,000 Dear Pharmacist letters were mailed in November 2002 and in January 2003. Additionally, in February 2003 a total of 25,000 outbound telephone calls were made to pharmacies and 15,000 of the callers requested a Dear Pharmacist letter. Finally, during the period between November 2002 and February 2003, GlaxoSmithKline representatives delivered 10,000 introductory packets that included the Dear Doctor Letter, an educational booklet on Lotronex, the physician's attestation form and product labeling.

Educational Booklets

GlaxoSmithKline has developed two education modules for physicians and pharmacists. These modules are entitled:

- *LOTRONEX (alosetron hydrochloride) Tablets: Understanding the Risks and Benefits*
- *Current Thinking About IBS: An Educational Review on Irritable Bowel Syndrome*

Both modules were reviewed and approved by the Division of Drug Marketing, Advertising and Communications (DDMAC). Physicians are encouraged to review these two modules before enrolling in the Prescribing Program for Lotronex. These modules can be obtained from the website www.lotronex.com, by forwarding a written request to GlaxoSmithKline, or by calling the Prescribing Program for Lotronex at 1-888-825-5249.

Other Outreach Programs by GSK

In 2003 GlaxoSmithKline initiated the following additional educational activities:

- ***Telephone Conference Series with Physicians***: These teleconferences cover the prescribing information and the Prescribing Program for Lotronex. The source materials for discussion is the module: *LOTRONEX (alosetron hydrochloride) Tablets: Understanding the Risks and Benefits.* Two rounds of this program were completed during 2003.

- ***Conventions***: GlaxoSmithKline maintained a booth at the American Gastroenterological Associations Convention (DDW) and the American College of Gastroenterology Convention in 2003; Discussions at the booth focused on the prescribing information and the Prescribing Program for Lotronex. The source material for discussion was the module: *LOTRONEX (alosetron hydrochloride) Tablets: Understanding the Risks and Benefits.*

- ***GI Specialty Sales Force***: A small targeted specialty sales force was launched in December 2003 and its role is to facilitate education on a local basis covering the prescribing information and the Prescribing Program for Lotronex.

- ***Speaker Program with Physicians***: These small local speaking engagements cover the prescribing information and the Prescribing Program for Lotronex. The source material for discussion is the module: *LOTRONEX (alosetron hydrochloride) Tablets: Understanding the Risks and Benefits.* The program is tentatively planned to start 2nd Qtr 2004.

Independent Programs

GlaxoSmithKline continues to provide grants to independent vendors to support educational programs. These independent programs focus on IBS and its treatment options.

Section II (C): RMP Evaluation: A Collaborative Research Program

Lotronex Collaborative Research Program Epidemiology Research Studies

Data Lock Points:

Claims-Based Observational Studies 09/30/03
Survey Program 12/31/03

Table of Contents

List of Tables

List of Figures

1. INTRODUCTION

An important aspect of the re-introduction of Lotronex is the Risk Management Program (RMP) for Lotronex, which was mutually agreed upon by the Food and Drug Administration (FDA) and GlaxoSmithKline (GSK). A primary component of the RMP is the evaluation of how effectively the program is working.

As part of this evaluation, GSK is conducting the following two epidemiology programs: the Lotronex Patient Follow-Up Survey Program (Survey Program) and a set of three longitudinal Claims-Based Observational Studies of people receiving prescriptions of Lotronex. RTI Health Solutions (RTI-HS) is conducting the Lotronex Patient Follow-Up Survey and is serving as the data coordinating center for the three Claims-Based Observational Studies. This report describes the current status of these four studies. It presents the results of the Survey Program through December 31, 2003 and the results of the Claims-Based Observational Studies through the third quarter of 2003 (from November 10, 2002 through September 30, 2003).

2. LOTRONEX PATIENT FOLLOW-UP SURVEY PROGRAM

2.1. Background

A primary component of the RMP for Lotronex is the Patient Follow-Up Survey Program. The Survey Program, launched in December 2002, is a prospective study of patients who are prescribed Lotronex and who voluntarily enroll at treatment initiation and are followed periodically throughout the duration of their use of Lotronex.

2.2. Objectives

This national study with quarterly follow-up was designed and implemented to address the following objectives:

3. Assess patient knowledge of the risks and benefits of Lotronex;
4. Assess patient behavior in relation to recommendations in the RMP; and

5. Assess the extent to which the patient satisfies the product labeling requirements for treatment with Lotronex.

2.3 Methods

2.3.1 Data Collection Methods

Patients who choose to enter the Survey Program may do so by completing a pre-enrollment card, which can be found in every Lotronex medication package or obtained from a prescribing physician. Once a patient completes a pre-enrollment card and sends it to the RTI data collection center, RTI assigns the patient a unique study identification (ID) number and mails a baseline packet consisting of a baseline questionnaire and cover letter, an informed consent form, and a $10 cash incentive. Patients are instructed to return the baseline questionnaire and signed consent form within seven days of receipt; however, they are given up to four weeks to return the forms before they are deactivated from the program due to non-response. If a patient returns a completed form after being deactivated, s/he is reactivated.

If a patient does not return the completed baseline questionnaire and signed consent form within two weeks, the RTI telephone operations unit then places a reminder call to the patient.

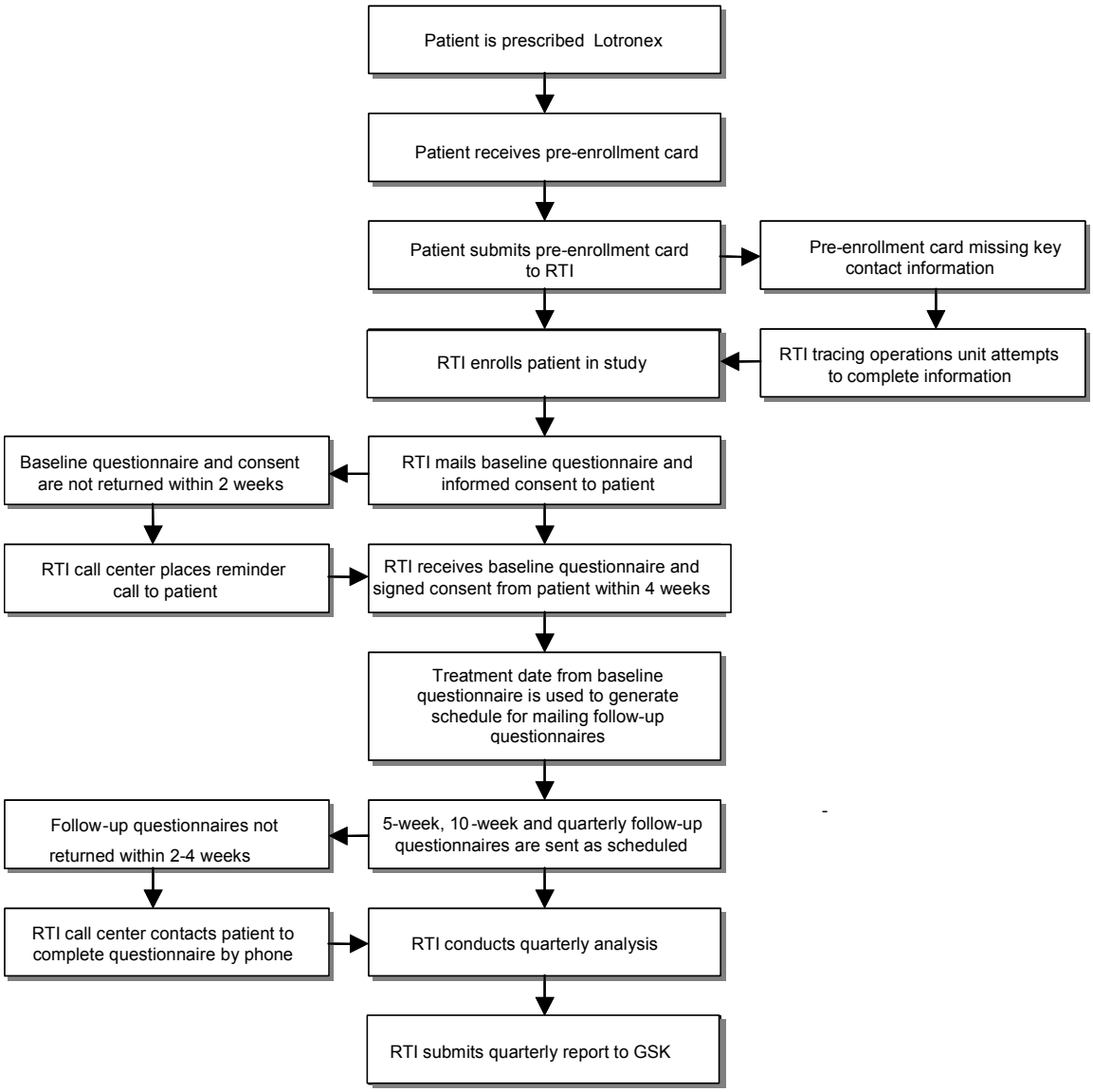
Patients who return a signed consent form and completed baseline questionnaire within the allotted timeframe become part of the Survey Program cohort and, as a result, are sent follow-up questionnaires five weeks and ten weeks after treatment initiation, and quarterly thereafter. These periodic follow-up assessments, which comprise a short questionnaire and $2 cash incentive, continue for as long as a patient is taking Lotronex and are willing to participate.

Data are collected primarily through mail questionnaires. However, in order to increase response rates, reminder calls are made to patients at each data collection interval if a completed questionnaire has not been received within two to four weeks. If desired, a patient can choose to complete any follow-up assessment via telephone rather than sending the hard copy questionnaire to the RTI data collection center. In addition, a toll-free hotline number is provided to Survey Program participants, which allows them to call the RTI data collection center during extended business hours with questions or to complete a follow-up assessment by telephone.

A variety of data are captured at each assessment. For example, the baseline assessment, which is the most comprehensive of the assessments, collects data about IBS history, prior symptoms, prior impact of IBS on quality of life, prior treatments, current dosage and frequency of Lotronex use, and the patient's interaction with the prescribing physician. The subsequent follow-up assessments include items about Lotronex dosage and frequency, and continued interaction with the prescribing physician.

A graphical overview of the data collection procedures for the Survey Program is presented in Figure 2-1.

Figure 2-1. Data Collection Flow Chart



2.3.1.a Modifications to the Baseline Questionnaire

Modifications to the existing survey instruments and to the newly developed items were evaluated earlier this year through a rigorous cognitive testing process. Results of the cognitive testing research and proposed modifications to the survey instruments were provided to the FDA under a separate cover. The revised survey instruments were implemented on December 1, 2003. For the purposes of this document,

the original baseline survey is referred to as Version 1 and the modified survey instrument is referred to as Version 2. The modifications to Version 1 of the questionnaire are as follows:

- Question 12 in Version 1 questionnaire asked the source of the medication guide and offered the response options of the physician or the pharmacist. Two new response options were added—the *Internet* and *never having received one*.
- A new question (question 10, Version 2) was added to assess how many tablets were being taken daily at the time of baseline questionnaire completion, since this number can be different from the number of tablets the patients were taking when they filled their prescriptions.
- In Version 1 (question 12), the response option for the question regarding why the doctor prescribed Lotronex was an open-ended text field. This response option did not lend itself to analysis. Therefore, the response options for this question were amended to *IBS* or *Other*. A text field is available for more details if *Other* is the chosen option.
- On Version 1 of the questionnaire, question 19 to assess IBS severity asked: "*Before Lotronex, how hard was it to work, spend time with family, etc. because of your IBS*?" This question was divided into the following two questions (questions 19 and 20, Version 2): "*Before Lotronex, did IBS make it difficult to lead a normal home/work life*?" and "*Before Lotronex, did IBS make it difficult to lead a normal social life*?"
- The following questions were added to assess the patients' understanding of the use of Lotronex (questions 22-27, Version2):
  - New or worsening pain in the bowels is a sign that a patient could be experiencing a serious problem related to Lotronex
    - True
    - False
    - Don't Know
  - If a patient experiences new or worsening pain in the bowels, which is the best action to take?
    - Continue taking Lotronex as prescribed
    - Lower the dose for a few days
    - Stop taking Lotronex, and call the Doctor
    - Don't Know
  - Blood in the stool is a sign that a patient could be experiencing a serious problem related to Lotronex

- True
- False
- Don't Know

- If there is blood in the stool, which is the best action to take?
  - Continue taking Lotronex as prescribed
  - Lower the dose for a few days
  - Stop taking Lotronex, and call the Doctor
  - Don't Know

- Constipation is a sign that a patient could be experiencing a serious problem related to Lotronex
  - True
  - False
  - Don't Know

- If a patient becomes constipated, which is the best action to take?
  - Continue taking Lotronex as prescribed
  - Lower the dose for a few days
  - Stop taking Lotronex, and call the Doctor
  - Don't Know

2.3.2 Statistical Methods

2.3.2.a Analysis

The analysis was performed according to the Statistical Analysis Plan (SAP) on file at RTI, with minor modifications. All categorical variables were described using univariate descriptive statistics (e.g., counts and percentages).

Questionnaire-Based Analysis

In previous reports, the univariate descriptive statistics for each assessment (e.g. baseline, week 5, week 10) have been presented. In this report, the cumulative data through the previous quarter, the data for the current quarter, and the total data are presented.

Patient-Based Analysis

In this report, responses at baseline are also presented, stratified by the following three groups: active users, those who discontinued Lotronex use, and those who are lost to follow-up.

"Active Users" are defined as study participants who are still participating in the study, who have been sent their most recent follow-up questionnaire

within four weeks from the end of the quarter, and who have not yet returned it by the data lock date. Patients in the "Discontinued Lotronex" category are those who have indicated that they stopped using Lotronex. The "Lost to Follow–up" category comprises all users who were sent a questionnaire more than four weeks before the end of the quarter and who have not yet returned it by the data lock date.

This patient-based analysis facilitates additional insight into compliance with the RMP by developing a clear picture of the patients who are retained in the study compared to those who discontinue Lotronex use or were lost to follow-up. The continuity of responses to certain questions asked at each assessment (e.g., talking to physicians about IBS symptoms, presence of a blue sticker on the prescription) will be evaluated.

Computation of Response Rates

Patients are allowed a 4-week window to complete the baseline and week 5 follow-up questionnaires, and an 11-week window to complete the week 10 and quarterly questionnaires. In order to take into account the lag time between delivery of a questionnaire to each subject and the return of the completed questionnaire, the response rate is calculated as the total number of patients who return the completed questionnaire among those whose data collection period for that particular follow-up (e.g., baseline, week 5, week 10, first quarterly) has expired.

Consequently, if a patient was sent a baseline questionnaire three weeks prior to the data lock date for this report (December 31, 2003), then the patient would not be included in the denominator for the calculation of the response rate because the data collection window had not closed by the appropriate data lock date.

Fulfillment of Eligibility Criteria

An algorithm was developed to assess whether a patient fulfilled all of the eligibility criteria for chronic, severe, diarrhea-predominant IBS based on the Lotronex labeling. The algorithm used questions relating to the reasons for taking Lotronex, clinical symptoms, duration, and disease impact.

Patients are considered to have met the eligibility requirements, as described in the label for Lotronex, if they meet the following criteria:

- Have IBS (Version 2 only), AND
- Have diarrhea, AND
- Have chronic IBS (e.g., ≥ 6 months), AND

- Have tried other treatments with no relief of symptoms, AND
- Have one or more of the following severity criteria:
  - Painful stomach cramps or bloating; or
  - Accidents or fecal incontinence; or
  - Restriction of daily living:
    - Somewhat or very hard to work, spend time with family, etc. (Version 1); or
    - Difficult to lead normal home/work or social life (Version 2).

2.3.2.b Adverse Events

Although adverse events are not solicited in the Survey Program, RTI does receive reports of adverse events from patients during the course of follow-up by mail or telephone. When a patient spontaneously reports an adverse event to RTI, RTI completes a standardized reporting form (with no identifying information) and forwards it to GSK's Global Clinical Safety and Pharmacovigilance group within two business days of receipt. For cases that GSK considers to be serious or of special interest, RTI requests authorization from the patient to allow GSK to contact the patient's physician for additional follow-up. If authorization is not obtained, further follow-up is not attempted.

2.4 Results

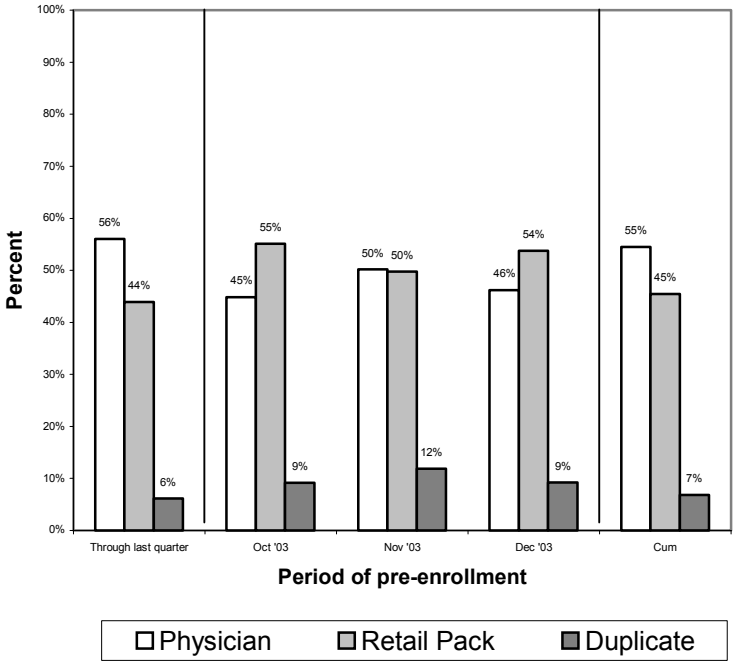
2.4.1 Pre-Enrollment

As of December 31, 2003, the RTI data collection center had received 4,032 pre-enrollment cards from a total of 3,701 unique patients (2,198 from physicians plus 1,834 from retail packs minus 277 duplicates minus 54 re-enrollment cards) and baseline responses from 3,219 patients. Using sales data it was estimated that 8,911 patients received a prescription of Lotronex in the US through the end of November 2003. By assuming a 4-week lag between obtaining a prescription and enrolling in the Survey Program, it is estimated that 42% (3,701/8,911) of all patients with a prescription for Lotronex pre-enrolled in the Survey Program and that 36% (3,219/8,911) completed a baseline questionnaire. Fifty-five percent of the pre-enrollment cards received were issued by the prescribing

physician's office. This estimate (which includes duplicates) indicates a higher rate of involvement by physicians than that observed in one other RMP in which only 20% of patients enrolled through the form provided by physicians (Mitchell, Van Benekom, & Louik, 1995). Figure 2-2 illustrates the monthly number of pre-enrollment cards by type, with duplicate cards included and broken out as a separate category.

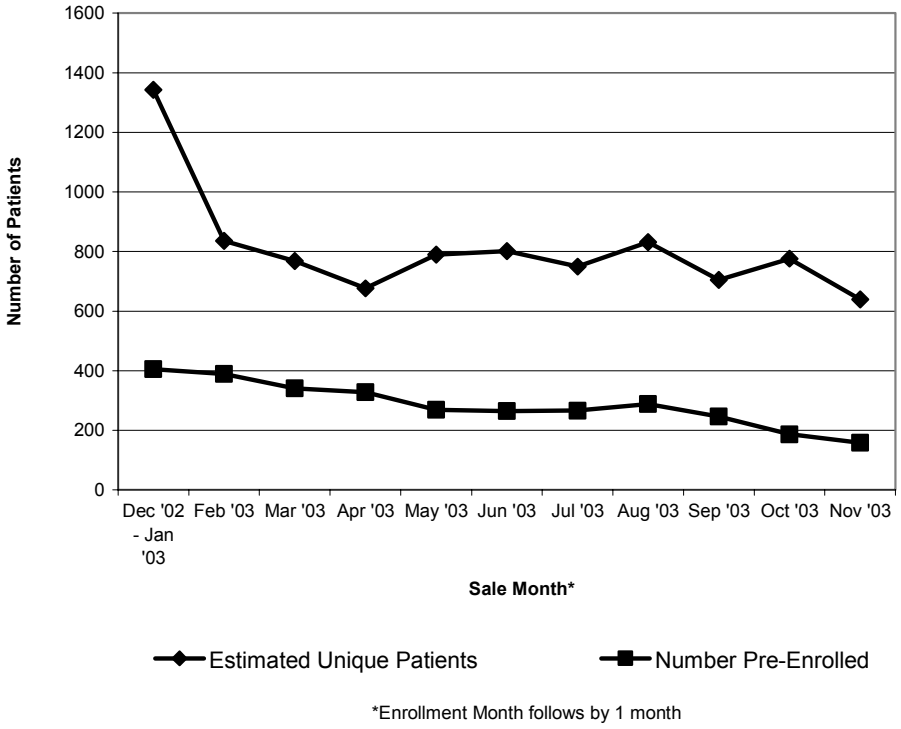
As expected, the majority of pre-enrolled patients were female (90%); however, 266 males (7%) also pre-enrolled in the program, and an additional 3% of subjects did not specify their gender. A total of 671 pre-enrolled patients (18%) were over the age of 65 years. Twenty-one patients under the age of 18 years pre-enrolled in the Survey Program.

Figure 2-2. Source of Pre-Enrollment Card



The monthly sales estimates patterns seem to match the pre-enrollment numbers for the subsequent month (Figure 2-3), with the exception of December 2003, in which the number of pre-enrollees was approximately 25% of the estimated sales for November 2003. This could be due to the holidays affecting patient enrollment in the study.

Figure 2-3. Monthly Patterns of Sales and Pre-Enrollment



2.4.2 Deactivation

Patients can become deactivated from the Survey Program for any of the following reasons:

- Non-response to the baseline questionnaire within a four-week period;
- Discontinuation of treatment;
- Refusal to participate; or
- Other miscellaneous reasons.

Patients who are deactivated from the Survey Program always have the opportunity to re-enroll in the program as long as they are taking Lotronex. Of the 3,701 patients who were pre-enrolled in the Program, 360 patients (10%) have currently been deactivated due to non-response to the baseline questionnaire. Eight-hundred seventy-eight patients (24%) have been deactivated because they have indicated that they no longer take Lotronex. Thirty-one patients (<1%) have been deactivated because they

no longer wished to participate. In total, 1,269 (34%) of pre-enrolled patients have been deactivated.

2.4.3 Baseline, Week 5, Week 10, and Quarterly Results

In the following results sections, for each assessment the percentages are based on cumulative denominators of all patients who provided non-blank responses. Table 2-1 below summarizes the number of patients responding to each assessment as of March 31, 2003; June 30, 2003; September 30, 2003; and December 31, 2003.

Table 2-1. Summary of Survey Responses—Cumulative Number of Responses

Patient Population	As of 3/31/03	As of 6/30/03	As of 9/30/03	As of 12/31/03
Pre-enrolled	1,357	2,296	3,112	3,701
Baseline	1,032*	1,907	2,595*	3,219
Week 5 follow-up	555	1,287	1,785	2,232
Week 10 follow-up	228	1,219	1,822*	2,339
Quarter 1 follow-up	0	304	1,198	1,766
Quarter 2 follow-up	0	0	267	1,082
Quarter 3 follow-up	0	0	0	216

*Earlier quarterly reports showed higher totals for each of these counts. In each case, a duplicate was identified after the report was completed and removed.

2.4.3.1 Response Rates

Table 2-2 presents the response rates for each assessment. Overall, the response rates were very high, ranging from 89% to 98%. As described in Section 2.3.2.a, response rates for each assessment (baseline, week 5, week 10, quarterly) are calculated as the total number of patients who return the completed questionnaire among those whose data collection period for that questionnaire has expired. Consequently, response rates for the third quarterly follow-up assessment could not be calculated at the time this report was written because the data collection window for patients who have received the third quarterly follow-up assessment was not closed as of December 31, 2003.

Table 2-2. Summary of Survey Response Rates[1]

Patient Population	Number of Questionnaires Sent[1]	Number of Questionnaires Completed and Returned[1]	Response Rate
Baseline respondents	3,559	3,174	89%
Week 5 follow-up respondents	2,247	2,186	97%
Week 10 follow-up respondents	2,047	2,001	98%
Quarter 1 follow-up respondents	1,388	1,354	98%
Quarter 2 follow-up respondents	527	515	98%
Quarter 3 follow-up respondents	N/A	N/A	N/A

2.4.3.2 Cumulative Baseline Results

As of December 31, 2003, 3,219 subjects completed and returned the baseline questionnaire. The response rate was 89% (3,174/3,559; see Table 2-2). The majority of participating patients are well-educated (72% with at least some college), Caucasian (97%), female (93%), and used Lotronex prior to its reintroduction in November 2002 (55%) (Table 2-3). Nineteen percent of all baseline respondents are over the age of 65 years (Figure 2-4). Twelve patients (ages 11 to 17 years) were less than 18 years old, and all twelve completed a baseline questionnaire (Figure 2-4). Of these, eight patients completed a week 5 questionnaire, six patients completed a week 10 questionnaire, five patients completed the Quarter 1 questionnaire, and three patients completed the Quarter 2 questionnaire. No patients who pre-enrolled under the age of 18 had completed the Quarter 3 questionnaire. While 26% of the women were obese, only 21% of the men were obese. This difference between women and men is consistent with the difference in the prevalence of obesity in the general population (Centers for Disease Control [CDC], 2003), although the

[1] The allotted timeframes for return of completed questionnaires for the baseline, week 5, week 10, and quarterly questionnaires are 4 weeks, 4 weeks, 11 weeks, and 11 weeks, respectively. Therefore, the numerators and denominators for the response rates calculation include only mailed questionnaires for which the allotted timeframe was completed by December 31, 2003.

percentages are lower than those of the general population (women, 35% and men, 32%). The regional distribution of patients is relatively even, with 24% of patients residing in the Northeast, 25% in the Southeast, 27% in the Midwest, and 24% in the West. Table 2-3 illustrates selected patient characteristics at baseline.

Figure 2-4. Age Distribution of Patients at Baseline (n =3,183 with known age)

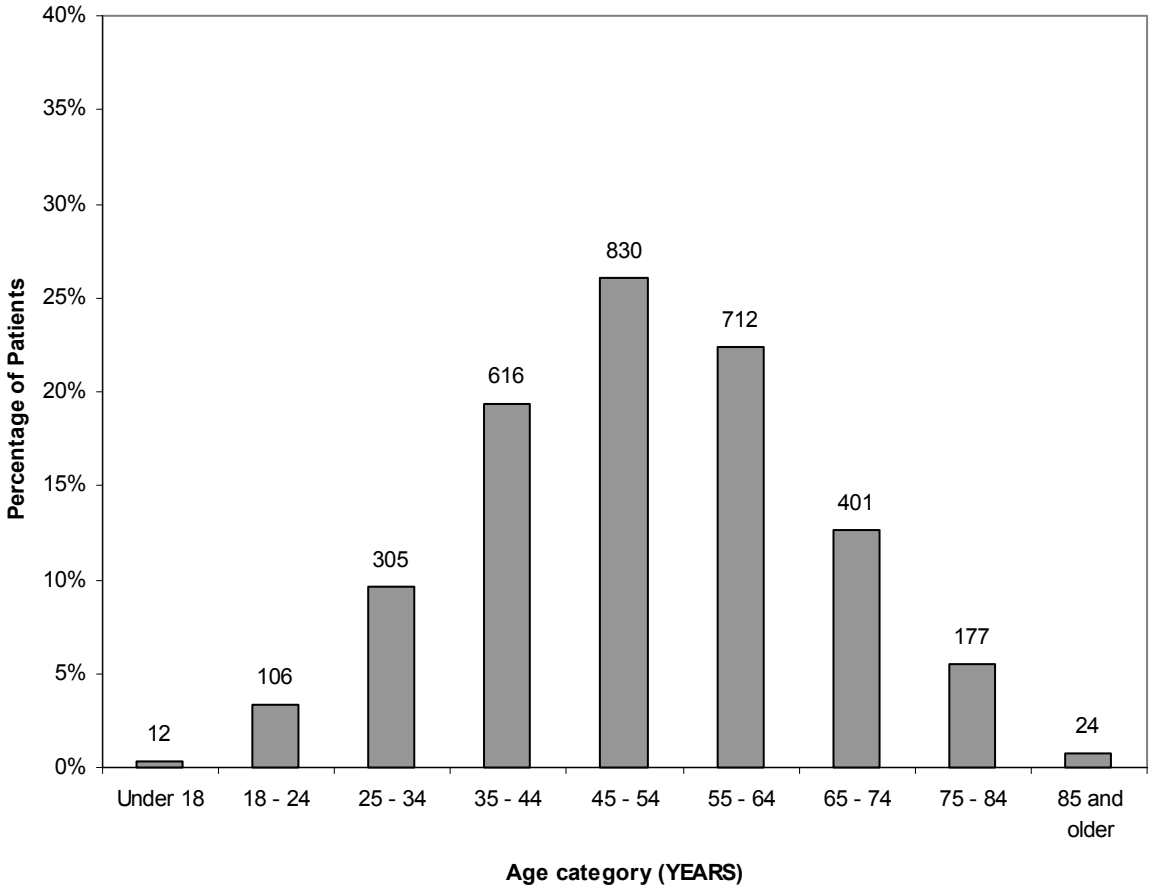


Table 2-3. Selected Patient Characteristics at Baseline

Patient Characteristic	N	Total responses*	%
Race: Caucasian	3,105	3,204	97
Gender: Female	2,913	3,128	93
Age: <18 years	12	3,183	0.4
Age: 18 – 44 years	1,027	3,183	32
Age: 45 – 64 years	1,542	3,183	48
Age: ≥65 years	602	3,183	19
At least some college education	2,277	3,184	72
Lotronex prescribed by gastroenterologist	2,306	3,199	72
Region: Northeast	785	3,219	24
Region: Southeast	807	3,219	25
Region: Midwest	862	3,219	27
Region: West	765	3,219	24
BMI >30 in women	734	2,855	26

*Refers to total non-blank responses.

Table 2-4 illustrates compliance rates with various aspects of the RMP at baseline. Eighty-seven percent of patients reported receiving a blue sticker with their prescription for Lotronex. An additional 9% did not know if they received the sticker.

Patients reported $\geq$ 90% compliance with all of the components of the RMP except for receiving a blue sticker on their prescription (87%). Table 2-4 provides information on each of the indicators of compliance with the RMP.

At baseline, patients were asked what their main bowel problem was. Ninety-four percent of the patients responded that diarrhea was their main bowel problem. Only one percent of patients reported constipation as their main problem. Of the 31 patients reporting constipation as their main problem, 20 patients (65%) have discontinued Lotronex use. Five percent (n=149) reported "other" as their main bowel problem. Seventy-one percent described their symptoms in detail, 29% emphasized the beneficial effect of Lotronex on their symptoms, and 1 subject reported ulcerative colitis. All symptoms are self-reported and not medically confirmed.

Table 2-4. Compliance at Baseline

Indicators of Compliance with RMP	N	Total responses*	%
Signed a Patient Physician Agreement	2,982	3,206	93
Discussed possible risks of Lotronex with doctor	3,083	3,199	96
Discussed with doctor how Lotronex can help	3,091	3,190	97
Discussed with doctor reasons to stop Lotronex	3,019	3,180	95
Discussed when to call the doctor	3,004	3,182	94
Received medication guide from doctor	2,880	3,166	91
Received medication guide from pharmacist	2,857	3,166	90
Read the medication guide (if received)	2,860	2,905	98
Received prescription with blue sticker	2,731	3,135	87

*Refers to total non-blank responses.

Table 2-5 shows compliance with patient eligibility criteria at baseline for women—who are specifically indicated for Lotronex use in the label—and men. Ninety percent of women met the full eligibility criteria of chronic, diarrhea-predominant, severe IBS, who failed conventional therapy.[2] Eighty-four percent of men in the study had also fulfilled the eligibility criteria to receive Lotronex . The percentage of patients reporting very severe symptoms is quite high, with 77% of all respondents reporting they had all 3 of the following conditions: 1) painful cramps and/or bloating, and 2) accidents or fecal incontinence, and 3) restriction of normal daily living because of IBS.

[2] The eligibility criteria algorithm for chronic, diarrhea-predominant, severe IBS is based on the symptoms and history questions in the baseline questionnaire. Patients were identified as eligible if they reported 1) Lotronex was prescribed for IBS (Version 2 of baseline questionnaire only), 2) diarrhea as the main problem, 3) IBS symptoms for six or more months, 4) other treatments were tried and did not work, and 5) one or more severity criteria (painful cramps or bloating, accidents or fecal incontinence, or restriction of daily living).

Table 2-5. Patient Eligibility Criteria Elements at Baseline in Females and Males

Baseline Compliance with Patient Eligibility Criteria	FEMALES N (%)	MALES N (%)
Met full eligibility criteria	2,296 (90)	153 (84)
Criteria for eligibility:		
Have diarrhea	2,596 (95)	173 (87)
IBS ≥ 6 months	2,795 (98)	206 (97)
Previous treatments for IBS	2,736 (96)	203 (96)
Inadequate relief of symptoms	2,592 (97)	192 (98)
Severity Conditions:		
Cramps or bloating	2,491 (87)	172 (81)
Accidents	2,672 (93)	189 (89)
Somewhat or very hard life (v1)**	2,772 (98)	202 (98)
Hard to lead normal home/work life (v2)***	57 (97)	6 (100)
Hard to live normal social life (v2)***	56 (95)	6 (100)
ALL 3 SEVERITY CONDITIONS (eligible patients only)	1,834 (80)	119 (78)

*Refers to total non-blank responses or classifiable (for eligibility criteria).

**Version 1 of the baseline survey instrument

***Version 2 of the baseline survey instrument

Of the subjects who started taking Lotronex at the time of their baseline assessment, 75% reported taking one tablet daily and 17% reported taking two tablets daily (Table 2-6). Of the small number of patients who discontinued Lotronex at baseline (n = 159), the median duration of use was 9 days.

Table 2-6. Characteristics of Lotronex Use at Baseline

Characteristics of Lotronex Use	N	Total responses*	%
Had taken Lotronex before November 2002	1,747	3,192	55
Started taking Lotronex	2,959	3,043	97
Taking one tablet daily	2,131	2,856	75
Taking two tablets daily	494	2,856	17
Other reported regimen	231	2,856	8
Median duration of use for those who discontinued treatment (days)	9	**159 valid stop dates	

*Refers to total non-blank responses.

**Valid stop date indicates that a complete date was given and that it was logically correct (that is, it fell between the "drug start date" and "today's date").

In order to address whether compliance with the RMP may reflect the high frequency of subjects who had used Lotronex prior to its reintroduction, we compared subjects who reported using Lotronex prior to November 2002 to those who reported not using it prior to November 2002. The distributions of the covariates in the baseline questionnaire were not notably different between the two groups. However, 67% of the prescribing physicians for previous users of Lotronex were gastroenterologists, compared to 79% for the Lotronex users with no history of use prior to November 2002.

2.4.3.3 Follow-Up Results (Weeks 5 and 10, Quarters 1, 2, and 3)

Overall

The percentage of patients with a history of Lotronex use before 2002 who responded to the surveys seemed to increase from week 5 (58%) to quarter 3 (78%) responses. The percentages of those taking one tablet daily decreased and those taking two tablets increased from week 5 (56% and 28%) to quarter 3 (46% and 36%) responses.

Week 5

As of December 31, 2003, 2,232 week 5 follow-up questionnaires had been received. The response rate was 97% (2,186/2,247; see Table 2-2). Table 2-7 describes characteristics of Lotronex use at each follow-up interval. Of those patients who filled a prescription for Lotronex in the previous 30 days (n = 1,358), 85% discussed their symptoms with the physician, 91% received a blue sticker on their prescription (indicating that the prescribing physician was in the PPL), and 6% did not know whether there was a blue sticker on the prescription. Fifty-six percent of patients were taking one tablet daily, and 28% were taking two tablets daily; 78% were taking Lotronex every day. Of the small number of patients (n = 281) who discontinued Lotronex, the median duration of use was 26 days, based on 238 valid responses for the date that Lotronex was discontinued.

Week 10

As of December 31, 2003, 2,339 week 10 follow-up questionnaires had been received. The response rate was 98% (2,001/2,047; see Table 2-2). One thousand seven hundred and forty-two patients (75%) reported having filled a prescription in the last 30 days. Of those filling a prescription, 89% had received a prescription with a blue sticker, 7% did not know if there was a blue sticker, and 81% had discussed their symptoms with their physician. Of those still taking Lotronex, 53% reported taking one tablet daily, and 30% reported taking two tablets daily. Of the 173 subjects who discontinued Lotronex, the median duration of use was 55 days, based on 157 valid responses for the date that Lotronex was discontinued.

Quarter 1

As of December 31, 2003, 1,766 Quarter 1 follow-up questionnaires had been received. The Quarter 1 questionnaire response rate was 98% (1,354/1,388; see Table 2-2). One thousand five hundred and forty-six patients (88%) reported having filled a prescription in the last three months. Of those filling a prescription, 91% had received a prescription with a blue sticker, 6% did not know if there was a blue sticker, and 78% had discussed their symptoms with their physician. Of those still taking Lotronex, 51% reported taking one tablet daily, and 30% reported taking two tablets daily. Of the 168 subjects who discontinued Lotronex, the median duration of use was 116 days, based on 130 valid responses for the date that Lotronex was discontinued.

Quarter 2

As of December 31, 2003, 1,082 Quarter 2 follow-up questionnaires had been received. The response rate was 98% (515/527; see Table 2-2). Nine hundred and sixty patients (89%) reported having filled a prescription in the last three months. Of those filling a prescription, 92% had received a prescription with a blue sticker, 5% did not know if there was a blue sticker, and 76% had discussed their symptoms with their physician. Of those still taking Lotronex, 48% reported taking one tablet daily, and 31% reported taking two tablets daily. Of the 77 subjects who discontinued Lotronex, the median duration of use was 196 days, based on 70 valid responses for the date that Lotronex was discontinued.

Quarter 3

As of December 31, 2003, 216 Quarter 3 follow-up questionnaires had been received. Quarter 3 questionnaire response rates could not be calculated at the time of this report because no patients' data collection window had yet closed. Two hundred and three patients (94%) reported having filled a prescription in the last three months. Of those filling a prescription, 96% had received a prescription with a blue sticker, 2% did not know if there was a blue sticker, and 77% had discussed their symptoms with their physician. Of those still taking Lotronex, 46% reported taking one tablet daily, and 36% reported taking two tablets daily. Of the 12 subjects who discontinued Lotronex, the median duration of use was 286 days, based on 10 valid responses for the date that Lotronex was discontinued.

Table 2.7, which follows, describes some characteristics of Lotronex use measured in the questionnaires from week 5 to Quarter 3.

Table 2-7. Characteristics of Lotronex Use at Week 5 Follow-Up, Week 10 Follow-Up, and Quarterly Follow-Up

Characteristics of Lotronex Use	Week 5	Week 10	Quarter 1 Response	Quarter 2 Response	Quarter 3 Response
Total	N= 2,232	N= 2,339	N= 1,766	N= 1,082	N=216
	% of Responses*				
Had taken Lotronex before re-introduction in November 2002	58	61	66	71	78
Still taking Lotronex (% of those providing follow-up)	87	93	91	93	94
Taking one tablet daily	56	53	51	48	46
Taking two tablets daily	28	30	30	31	36
Other reported regimen	16	18	19	21	18
Taking Lotronex every day	78	78	77	76	87
Taking Lotronex some days	22	22	23	24	13
	(n / non-blank responses)				
Still taking Lotronex	1,938/2,219	2,163/2,336	1,593/1,761	1,003/1,080	204/216
	Days				
Median duration of use (days) for those who have discontinued treatment	26	55	116	196	286

*Refers to non-blank responses.

2.4.3.4 Loss to Follow-Up

When comparing the frequency of those who completed the follow-up questionnaires to those who did not respond, most baseline responses differed by less than one percent. History of use of Lotronex before 2002 was consistently greater for those returning the questionnaires than for those not returning questionnaires.

2.4.4 Patient-Based Analysis Results

We stratified the baseline characteristics of the study participants, based on their status in the study (active, discontinued use of Lotronex, and lost to follow-up).

For the most part, there were no significant differences in the distribution of the responses to the baseline questionnaire. Table 2-8 presents some descriptive variables used to evaluate basic demographics, compliance, and eligibility.

Table 2-8. Selected Patient Characteristics at Baseline

Patient Characteristics at Baseline	Active	Discontinued Lotronex Use	Lost to Follow-Up
TOTAL	2,307	842	70
DEMOGRAPHICS	**N (%)**	**N (%)**	**N (%)**
Caucasian	2,223 (96)	818 (97)	64 (91)
Female	2,108 (94)	741 (91)	64 (93)
At least some college education	1,646 (72)	587 (70)	44 (66)
Had taken Lotronex before November 2002	1,388 (61)	334 (40)	25 (37)
Constipation at baseline	13 (1)	18 (2)	0 (0)
COMPLIANCE			
Signed a Patient Physician Agreement	2,146 (94)	772 (92)	64 (91)
Discussed the possible risks with doctor	2,223 (97)	792 (95)	68 (99)
Prescription had blue sticker	1,971 (88)	696 (84)	64 (94)
ELIGIBILITY			
Met all eligibility criteria	1,853 (91)	614 (85)	52 (85)
Criteria for eligibility:			
Have diarrhea	2,063 (95)	723 (92)	61 (94)
IBS >6 months	2,224 (98)	796 (96)	69 (100)
Previous treatments for IBS	2,175 (96)	780 (94)	68 (99)
Inadequate relief of symptoms	2,073 (97)	731 (96)	62 (94)
Severity Conditions:			
Cramps or bloating	1,975 (87)	705 (85)	58 (85)
Accidents	2,128 (93)	753 (90)	60 (90)
Somewhat or very hard life (v1)	2,186 (98)	808 (98)	67 (99)
Hard to lead normal home/work life (v2)	62 (97)	2 (100)	N/A
Hard to live normal social life (v2)	60 (95)	3 (100)	N/A
ALL 3 SEVERITY CONDITIONS (eligible patients only)	1,489 (80)	473 (77)	42 (81)

*Refers to total non-blank responses.

The percentage of patients with a history of Lotronex use before 2002 is significantly greater among active users (61%) compared to those who discontinued Lotronex use and those lost to follow-up (40% and 37%, respectively).

2.4.5 Follow-Up Time

Sixty-two percent of patients who discontinued use of Lotronex (n = 842) did so in the first 60 days from their initial dispensing. Sixty-eight percent of active users (n = 2307) have between 150 and 420 days of follow-up time available. The follow-up time of the patients lost to follow-up (n = 70) is evenly distributed (Figure 2-5). Table 2-9 presents the average follow-up time.

Figure 2-5. Follow-Up Time Distribution

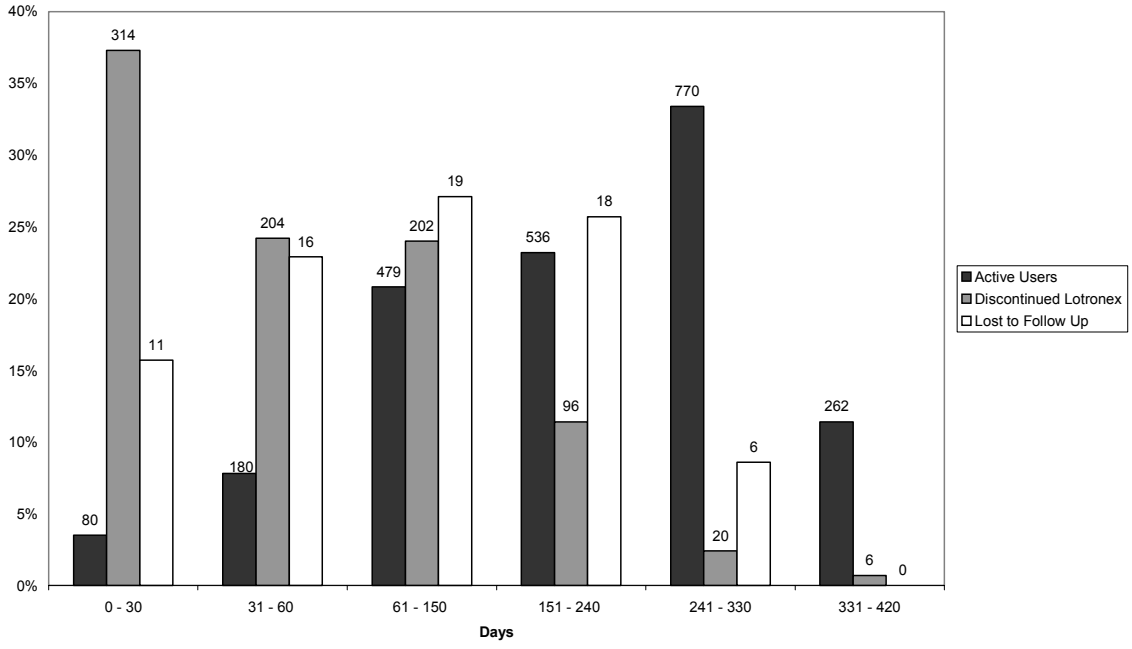


Table 2-9. Follow-Up Time by Latest Survey

	Active	Discontinued Use of Lotronex	Lost to Follow-Up
Last Survey Received	N* (%)	N (%)	N (%)
Baseline	156 (7)	169 (20)	20 (29)
Week 5	135 (6)	259 (31)	14 (20)
Week 10	460 (20)	167 (20)	15 (21)
Quarter 1	528 (23)	159 (19)	17 (24)
Quarter 2	767 (33)	76 (9)	4 (6)
Quarter 3	261 (11)	12 (1)	0 (0)
Average Follow-Up Time By Last Survey Received (days)	Average	Average	Average
Baseline	51	18	62
Week 5	48	28	49
Week 10	84	58	92
Quarter 1	168	125	173
Quarter 2	259	197	258
Quarter 3	350	313	N/A
Overall Average Follow-Up Time	187	70	104

*Number of patients for whom the last survey was the one listed in the rows

2.4.6 Adverse Event Reports

Through December 31, 2003, 217 adverse events (including lack of efficacy and constipation) have been reported through the Survey Program. The reports are from 207 unique patients.

The majority of reports to date have not been considered serious. As of December 31, 2003, GSK had requested follow-up of 21 adverse events reported through the Survey Program, and ten patients had authorized follow-up. A complete discussion of adverse events will be addressed by the Post-Marketing Surveillance by GSK.

Two deaths unrelated to Lotronex have been reported through the Survey Program. Consequently, the follow-up process has been modified to account for such cases. Specifically, the telephone interviewers have been trained to ask any person reporting the death of a subject to provide their understanding of the cause of death.

2.5 Discussion

2.5.1 Participation

By assuming a 4-week lag between obtaining a prescription and enrolling in the Survey Program, it is estimated that 42% (3,701/8,911) of all patients with a prescription for Lotronex pre-enrolled in the Survey Program and that 36% (3,219/8,911) completed a baseline questionnaire. This enrollment rate is comparable to other national study data. The pattern of enrollment seems to match the pattern of use estimated on sales for Lotronex in 2003, with monthly enrollment rates ranging between 25% and 49% of the estimated monthly new users.

2.5.2 Patient Characteristics

The baseline information about patient and symptom characteristics indicates that patients receiving Lotronex are indeed meeting the patient eligibility criteria established for the product. Ninety percent of female patients met the eligibility criteria in the label for Lotronex. That is, they had symptoms consistent with diarrhea-predominant IBS, had IBS for six months or longer, had IBS not relieved by other treatments, and had at least one symptom of severity. Eighty-four percent of the male patients also met the eligibility criteria.

The data from the Survey Program indicate that the patients receiving Lotronex are at the severe end of the IBS spectrum, with 80% of the eligible patients fulfilling all three severity criteria, and only 1.4% of the eligible patients having only one of the severity criteria. This may be an indication that physicians are being conservative in their prescribing practices for Lotronex, or that the more severe patients choose to use Lotronex. It may also indicate that patients who participate in the Survey Program tend to be those with more severe symptoms.

Over 90% of patients reported that the disease had a significant impact on their daily lives, and that the symptoms were severe.

Most patients (94%) reported diarrhea as their main bowel problem, and only one percent of patients reported constipation. Sixty-five percent of the 31 patients who indicated constipation as their main bowel problem subsequently discontinued use of the drug. The extent to which their

constipation was severe or chronic (contraindications of Lotronex) versus a normal part of their symptom fluctuation in IBS is unknown.

Seventy-one percent of patients who discontinued Lotronex did so by week 10, with an average follow-up time of 70 days.

2.5.3 Elements of the Risk Management Program

The results of the patient Survey Program suggest that patients are actively engaging with their physicians about the RMP. Over 90% of patients report having a discussion with their physician about risks and benefits, receiving and reading the medication guide, and signing the PPA form. These data, coupled with the high education level of participating patients and the high response rate in the Survey Program, indirectly suggest that these users of Lotronex are knowledgeable about the risks and benefits of Lotronex.

Starting December 1, 2003, Version 2 of the baseline questionnaire, which includes additional questions to directly assess patient knowledge of risks and benefits, was implemented. Although the sample size of returned questionnaires is fairly small (n = 68), over 90% of the patients responded correctly to six out of seven questions. When asked about the best action to take if constipation occurs, 82% of patients indicated they would stop the use of Lotronex and call the doctor as recommended in the Medication Guide, and 15% of patients answered that they would lower the dose of Lotronex instead.

Compliance with the elements of the RMP was high among study respondents. Specifically, at baseline, the high rates of compliance (>90%) with the use of the PPA, use of the medication guide, and appropriate dialogue between patient and physician suggest that these aspects of the RMP are working well. The percentage of prescriptions with blue stickers remained consistently high in all assessments from baseline through Quarter 3 (range, 87%−96%).

The percentage of patients receiving information regarding IBS symptoms decreased slightly from 85% at week 5 response to 77% at Quarter 3 response.

2.5.4 Key Learnings

A procedure for reviewing reported cases of potential adverse events and following up on key cases when patient consent is granted has been implemented. This process has been underway for several months and is working well.

As of December 1, 2003, six new questions have been added to the baseline questionnaire to assess the patients' understanding of the medication guide. Though the sample size is still small (n = 68), most patient responses to the new questions demonstrated excellent understanding.

Data indicate that 80% of the eligible female patients in the Survey Program have very severe IBS, i.e., suffer from all three severity symptoms, while the label for Lotronex indicates that only one severity symptom is required (coupled with the other eligibility factors) for a patient to be eligible for Lotronex. This may be an indication of conservative physician prescribing patterns for Lotronex or an indication of the types of patients who choose to use Lotronex.

During the last year, baseline compliance to measures of adherence to the RMP (signed PPA, presence of a blue sticker, discussion of symptoms with a physician, and reading of the medical guide) remained very high. As duration of use increases, there has been a decline in the percentage of patients speaking to their physicians about their symptoms before the latter dispensings.

The percentage of enrollees in December was lower than in previous months (25%). This could be due to the holidays affecting patient enrollment in the study.

2.5.5 Conclusion

The Survey Program has successfully followed 3,219 patients who have used Lotronex. Results pertaining to patient awareness, compliance with aspects of the Lotronex RMP, and concordance between patient characteristics and program guidance all suggest that the aspects of the RMP being measured in this study continue to work well. Questions assessing the patients' knowledge of the information provided in the medication packet that were added to the baseline questionnaire will allow

more accurate evaluation of the objectives specific to patient knowledge of the risks and benefits of Lotronex. Finally, continuation of the patient-based analysis will allow more in-depth analysis of specific variables of interest.

3. CLAIMS-BASED OBSERVATIONAL STUDIES

3.1 Background

As outlined in the June 7, 2002 approval letter, GSK is undertaking several post-marketing commitments. One of these commitments is the Epidemiologic Program for the Study of the Safety and Utilization of Lotronex in the US. This program includes a set of longitudinal Claims-Based Observational Studies, the objectives of which are to:

- Describe and characterize patients who receive Lotronex;
- Describe and characterize compliance with the PPL as measured by the presence of a signed PPA in the patient medical record;
- Determine the incidence of events of special interest[3] in patients treated with Lotronex and in a comparison group of patients;
- Determine the incidence of events of special interest in patients receiving Lotronex for longer than six months and in a comparison group;
- Determine the incidence of the events of special interest in patients over the age of 65 receiving Lotronex and in a comparison group; and
- Determine risk factors for the events of special interest.

The principal investigators for this program are Dr. Jerry Avorn, Dr. Jerry Gurwitz, and Dr. Alec Walker. The investigators are conducting the studies independently at their respective sites, while frequently meeting as a team to ensure that scientific methods and study operational definitions are consistent across sites. Table 3-1 highlights the investigators and the database sources being utilized for these studies. RTI-HS serves as the coordinating center for the sites.

[3] For purposes of this study, "events of special interest" are (1) colon ischemia (CI), (2)complications of bowel motor dysfunction (BMD), and (3) bowel surgery (BS).

Because the number of identified Lotronex users is very low, each study is currently providing descriptive data until sample sizes are adequate to assess the primary objectives of the program. At that time, more detailed analyses will be conducted as specified in the statistical analysis plan (SAP).

Table 3-1. Principal Investigators and Database Sources for Claims-Based Observational Studies

Investigator	Database Source	Comments/Size
Dr. Walker	Ingenix Database	The Ingenix Database comprises approximately 4.2 million insured patients.
Dr. Avorn	PA PACE Program NJ Medicaid and PAAD Programs	The PACE program comprises approximately 221,000 patients over the age of 65 and is linked to Medicare similar to the NJ Program. The NJ Program comprises approximately 200,000 patients over the age of 65 years. Of these, approximately 65% are from PAAD and 35% are from Medicaid.
Dr. Gurwitz	HMO Research Network Center for Education Research on Therapeutics (CERT)	3.9 million insured ▪ Harvard Pilgrim Health Care (Approximately 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 (Approximately 2,000 Medicare paid) ▪ Lovelace Health Systems (Albuquerque, NM)

The RTI-HS coordinating center team, performing quality control checks and preparing the combined report, works according to established standard operating procedures and project-specific work practice documents when managing information submitted by the investigators. Periodic project reviews and internal quality assurance audits are conducted to ensure compliance with these procedures. RTI-HS's role in the Claims-Based Observational Studies was approved by the RTI

Institutional Review Board (IRB), and undergoes annual review. Each investigator site has also undergone a thorough IRB review and approval process specific to their institution.

3.2 Methods

Each study utilizes automated health insurance claims, definitional algorithms, and medical records from the research databases. A description of each data source is included below.

3.2.1 Ingenix Database

The Ingenix Database holds data from the second largest healthcare company in the US, with over 300,000 physicians contracted to provide healthcare coverage to over 14 million members. The Research Database comprises patients who have both medical and prescription coverage and includes nearly 8 million persons as far back as 1990. Approximately 4.2 million persons are recorded in the Research Database in 2002. The Research Database currently includes information from 29 affiliated health plans from 19 states.

3.2.2 Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE) and New Jersey Pharmaceutical Assistance for the Aged and Disabled (PAAD) Program

The PACE program comprises approximately 221,000 participants over the age of 65 years. The participants receive financial assistance for prescription pharmaceuticals and other healthcare items. The prescription data can be linked to Medicare Parts A and B claims. These claims include all hospitalizations, physician visits, recorded diagnoses, nursing home stays, procedures, laboratory tests, and other measures of healthcare utilization.

The PACE program covers all medications that require a prescription in the Commonwealth, as well as insulin, insulin syringes, and insulin needles (unless a manufacturer does not participate in the Manufacturers' Rebate Program). It does not cover experimental medications or any

medications that can be purchased without a prescription. Beneficiaries are required to pay a $6 co-payment for each prescription.

The PAAD program, which was established in 1975, is the oldest state-funded prescription program in the country. The co-payment is $5 per prescription. Nearly 200,000 New Jersey residents are enrolled in PAAD. To be eligible for this program, a beneficiary must be a New Jersey resident 65 years of age or older, or be receiving Social Security Disability benefits and have an annual income of less than $19,739 if single, or less than $24,203 if married. The average senior on PAAD receives approximately 33 prescriptions per year, averaging $59.79 per prescription, for an average annual benefit of $1,973. The PAAD program also helps eligible New Jersey residents purchase prescription drugs, insulin, insulin supplies, diabetic testing materials, and needles used in the treatment of multiple sclerosis and other diseases.

3.2.3 HMO Research Network CERT

The HMO Research Network Center for Education and Research on Therapeutics (CERT) includes ten HMOs that collaborate to facilitate public domain research that takes advantage of the HMOs' defined populations; their detailed information about their members, their members' health status and healthcare; their providers; and the HMOs' ability to intervene to improve care. Nine of the ten HMO sites are participating in this study. Together, the organizations participating in this study are responsible for the healthcare of approximately 3.9 million individuals in all regions of the country. In all plans of the network, more than 59,000 physicians, including nearly 16,000 primary-care providers in over 1,000 sites, provide care. These health plans serve diverse populations, with the percentage of African-American members as high as 33% in some HMOs, the percentage of Hispanic members as high as 38%, and the percentage of Asian members as high as 13%. All serve Medicaid and Medicare beneficiaries, as well as commercially insured members. These plans also represent a variety of managed-care organizational models, including staff model, group, network, and individual practice association (IPA) systems. Individual HMOs in this group have up to 69% of their members in networks, while others have up to 66% in IPAs.

3.2.4 Identification of Cohorts

Each Claims-Based Observational Study utilizes healthcare claims and abstraction of medical records to identify and study patients who receive Lotronex (known as the Lotronex user group), as well as patients who are similar and do not receive Lotronex (the non-Lotronex comparator group). The study involves the collection of both retrospective and prospective data derived from claims and medical records to meet the study objectives.

The methods used to achieve the first two objectives of the database studies are described below. The methods outlining how the remaining objectives will be met will be included in subsequent reports, as relevant results become available.

Objective 1. Characterize patients who receive Lotronex

Users of Lotronex were determined by a computer-coded dispensing of Lotronex from a pharmacy. The date of the first prescription serves as the index date for each user of Lotronex. The comparison group is matched to Lotronex users by their characteristics at the time of the index date. All patients must have at least one pharmacy-dispensing claim with an NDC code for Lotronex to be considered a user of Lotronex. The demographic characteristics and healthcare utilization of users of Lotronex are described.

Objective 2. Determine compliance with PPL as measured by the PPA for Lotronex

Medical records are being abstracted to determine the presence of a signed PPA form. Each site examines approximately 25% of users to determine whether a signed copy of the PPA is in the patient's medical record.

3.3 Results

3.3.1 Progress to Date

This report covers the dispensing of Lotronex through the third quarter of 2003. A total of 121 users (40 new users) received a prescription for Lotronex between October 1, 2002 and September 30, 2003.

The results to date for each claims-based study are summarized in Table 3-2. The table presents the number of users of Lotronex identified as of September 30, 2003 (September 15, 2003 for the HMO Research Network CERT).

Table 3-2. Progress as of September 30, 2003, in the Three Claims-Based Observational Studies of Lotronex

Database Source	Status
PA PACE Program/NJ Medicaid and PAAD Program	Identified 4 users of Lotronex (PACE)/ Results not yet available (NJ PAAD)
HMO Research Network CERT	Identified 28 users of Lotronex
Ingenix Database	Identified 89 users of Lotronex

A total of 121 users with a total of 277 dispensings were identified. Approximately 89% were females, and most patients were between the ages of 25 and 54 years.

Forty percent of the cumulative dispensings occurred in the Southeast, and 29% occurred in the Midwest. The remaining dispensings were evenly distributed in the Northeast and West.

Cumulatively, 69% of the first dispensings were prescribed by a gastroenterologist, with a slight reduction to 64% for additional dispensings. In the current quarter, 4% of the first dispensings and 5% of subsequent dispensings could not be stratified by physician type.

Cumulatively, 50% of all users had only one dispensing, and 16% had two dispensings. Twenty-nine percent of the patients to date had a total of 30 tablets dispensed, with another 25% receiving a total of 60 tablets.

Two potential contraindications (diverticulitis and ulcerative colitis) were found for new users during Quarter 3, 2003. Three diagnosis codes were found for potential contraindications in previous quarters: intestinal obstruction, diverticulitis, and thrombophlebitis. Contraindications for up to two years prior to the dispensing of Lotronex were reviewed. The average look-back time for the users of Lotronex was 1.38 years. These potential contraindications are not confirmed by medical record review.

Results on verifying compliance with the PPA were available from the Ingenix Research Database (from Quarter 4, 2002 to Quarter 3, 2003) and the HMO Research Network CERT (from Quarter 4, 2002 to Quarter 1, 2003). All of the 29 charts sought for review this quarter were identified and 69% (n =20) of the charts contained a PPA signed by both the

physician and the patient. Overall, 70% of all charts identified had a PPA signed by both patient and physician.

3.4 Discussion

A total of 121 users of Lotronex who were prescribed Lotronex between November 2002 and September 2003 were identified. The chart retrieval success rate was 89% (91/102). We established that 70% (64/91) of the records contained a PPA signed by both the physician and the patient. The success rate in retrieving charts has increased from previous reports as a result of the efforts taken to educate physicians who are concerned about the HIPAA privacy regulations set in place after April 14, 2003.

Medical record abstractions are currently underway for the six potential events of special interest (3 among the users of Lotronex and three among the comparator cohort) among five unique patients (2 among the users of Lotronex and three among the comparator cohort) identified previously.

Using available data, it can be inferred that Lotronex patients and their physicians are completing the PPA as recommended by the FDA. Even though there is often a long lag time to update all documents into a medical record, 70% of the records reviewed have a PPA.

4. SUMMARY OBSERVATIONS

Two components of the risk management program for Lotronex, the Survey Program and the Claims-Based Observational Studies, complement each other well and provide different and important insights about the patients who are receiving Lotronex and how the RMP is working. The primary strengths of the Survey Program are attainment of real-time data and attainment of information about physician–patient interactions. Complementing the Survey Program, the Claims-Based Observational Studies provide an objective method to evaluate the experience of patients who receive Lotronex, independent of other factors that might influence patient participation or reporting.

The information on patient and symptom characteristics at baseline indicates that patients receiving Lotronex are indeed meeting the criteria established for users of the product. Most patients are fulfilling all of the

eligibility criteria for severe IBS. Moreover, these patients report a significant impact of the disease on their daily lives.

Compliance with elements of the RMP for Lotronex was high, as indicated by high percentages of patients discussing the risks and benefits of using Lotronex with their physicians and signing the PPA. The high rates of compliance (>90%) seen in the Survey Program, such as the use of the PPA, use of the medication guide, appropriate dialogue between patient and physician, and the nature of the IBS being treated, all suggest that these aspects of the RMP continue to work well.

The fact that most eligible patients meet all three severity criteria, with the requirement being that only one severity criterion needs to be met, seems to indicate conservative prescribing practices and/or patient self selection. The patients participating in the survey seem to be severely affected. Both the Survey Program and the Claims-Based Observational Studies show a higher percentage of gastroenterologists prescribing Lotronex than other physicians. The number of records with a signed PPA in the Claims-Based Observational Studies was 70%, while in the Survey Program, 93% of the patients say they signed a PPA. The difference between the two figures may reflect that the Claims-Based Observational Studies analysis numbers can be affected by the delay in paperwork being filed in the medical record, while the Survey Program measures the action as recalled by the study participants.

Finally, the number of users of Lotronex identified in the Claims-Based Observational Studies still remains small (n = 121), and different time periods and study populations are covered in the Survey Program and Claims-Based Observational Studies. Therefore, comparisons of results from the two approaches should be made cautiously.

5. REFERENCES

CDC (2003). *Overweight Prevalence*. Retrieved December 30, 2003, from http://www.cdc.gov/nchs/fastats/overwt.htm

Mitchell, A., Van Benekom, C., & Louik, C. (1995). A pregnancy prevention program in women of childbearing age receiving isotretinoin. *New England Journal of Medicine*. *333*(2), 101-106

Roche Laboratories, Inc. (2002). *New prescribing procedures for Accutane as of April 10, 2002*. Retrieved June 11, 2003, from http://www.rocheusa.com/products/accutane/accutane_prescriber.pdf

Section II(D): Post-Marketing Surveillance

Section II(D): Post-Marketing Surveillance

Numbers of Cases

As of February 6, 2004, GSK had received 127 post-marketing AE reports (cases) involving patients who received alosetron after re-introduction of the product. Twenty-nine (23%) of the 127 reports were received via the Lotronex Patient Follow-Up Survey Program (EPI-40255). Each case was entered into the GSK safety database and was reported to FDA in accordance with the provisions of 21 CFR 314.80 and the June 7, 2002 approval letter. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Among the 127 post-marketing cases:

- 76 (60%) were received from consumers;
- 37 (29%) were assessed as "serious" under the provisions of 21 CFR 314.80(a) (FDA Form 3500A Section C) and/or were considered medically serious by GSK; and
- 114 (90%) involved female patients.

Where exact age was specified (77 cases), the median patient age was 55 years (range, 16-82 years). Where exact or approximate age was specified (81 cases), 19 cases (23%) involved patients ≥65 years of age or with age reported as "elderly".

Adverse Event Cases by System Organ Class

The 127 post-marketing cases contain a total of 285 AEs. The distribution of reported AEs by system organ class is shown in Table 1.

Table 1. Distribution of AEs by System Organ Class
All Post-marketing Cases

System Organ Class	Number (%) of Events	Number of Cases*
Gastrointestinal disorders	136 (47.7%)	77
General disorders and administration site conditions	56 (19.6%)	49
Nervous system disorders	20 (7.0%)	12
Psychiatric disorders	10 (3.5%)	7
Investigations	9 (3.1%)	8
Reproductive system and breast disorders	7 (2.5%)	6
Respiratory, thoracic and mediastinal disorders	7 (2.5%)	6
Skin and subcutaneous tissue disorders	7 (2.5%)	6
Injury, poisoning and procedural complications	6 (2.1%)	6
Musculoskeletal and connective tissue disorders	6 (2.1%)	4
Cardiac disorders	5 (1.8%)	4
Infections and infestations	4 (1.4%)	3
Eye disorders	3 (1%)	3
Metabolism and nutrition disorders	2 (<1%)	2
Blood and lymphatic system disorders	1 (<1%)	1
Hepatobiliary disorders	1 (<1%)	1
Immune system disorders	1 (<1%)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (<1%)	1
Pregnancy, puerperium and perinatal conditions	1 (<1%)	1
Renal and urinary disorders	1 (<1%)	1
Vascular disorders	1 (<1%)	1
Total	285	

***This column shows the number of cases with at least one event coded to each system organ class. Many cases contain multiple events; thus, the total for this column is greater than the total number of cases.**

Events with 3 or more reports (≥1% of total number of events) are as follows:

Gastrointestinal disorders: Abdominal distension, Abdominal pain, Abnormal feces, Colitis ischemic, Constipation, Diarrhea, Fecaloma, Feces discolored, Irritable bowel syndrome, Nausea, Rectal hemorrhage, Vomiting.
General disorders and administration site conditions: Asthenia, Drug ineffective, Pharmaceutical product complaint.
Investigations: Weight decreased.
Nervous system disorders: Headache.

Summary: Review of these post-marketing reports does not highlight any new safety issues.

Serious Adverse Event Cases

Thirty-seven (29%) of the 127 post-marketing cases were considered "serious" under the provisions of 21 CFR 314.80(a) and/or were considered medically serious by GSK.
It is important to note that at GSK, the seriousness of post-marketing AEs is assessed at the case, rather than the event, level. It is thus inappropriate to describe each individual AE reported in these "serious cases" as "serious events."
The 37 serious cases contained a total of 114 AEs. The distribution of AEs reported in these cases, by system organ class, is shown in Table 2.

Table 2. Distribution of AEs by System Organ Class
Serious Post-marketing Cases

System Organ Class	Number (%) of Events	Number of Cases*
Gastrointestinal disorders	61 (53.5%)	27
Nervous system disorders	12 (10.5%)	5
General disorders and administration site conditions	7 (6.1%)	6
Investigations	6 (5.3%)	5
Respiratory, thoracic and mediastinal disorders	5 (4.4%)	4
Psychiatric disorders	4 (3.5%)	3
Reproductive system and breast disorders	3 (2.6%)	3
Skin and subcutaneous tissue disorders	3 (2.6%)	2
Cardiac disorders	2 (1.8%)	2
Infections and infestations	2 (1.8%)	2
Metabolism and nutrition disorders	2 (1.8%)	2
Injury, poisoning and procedural complications	1 (<1%)	1
Musculoskeletal and connective tissue disorders	1 (<1%)	1
Eye disorders	1 (<1%)	1
Blood and lymphatic system disorders	1 (<1%)	1
Hepatobiliary disorders	1 (<1%)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (<1%)	1
Renal and urinary disorders	1 (<1%)	1
Immune system disorders	0	0
Pregnancy, puerperium and perinatal conditions	0	0
Vascular disorders	0	0
Total	114	

***This column shows the number of cases with at least one event coded to each system organ class. Many cases contain multiple events; thus, the total for this column is greater than the total number of serious cases.**

Summary: Review of these serious post-marketing reports does not highlight any new safety issues.

Reports of pregnancy

Alosetron is classified in Pregnancy category B under the provisions of 21 CFR 201.57(f)(6). Reproduction studies in rats and rabbits have revealed no evidence of harm to the fetus due to alosetron. There are, however, no adequate and well-controlled studies of alosetron in pregnant women. As with other medicines, alosetron should not be used in pregnancy unless the expected benefit to the mother outweighs any potential risk to the fetus. It has been the policy of GSK to collect data on all reports of pregnancy occurring during the administration of its products.
Following product re-introduction, GSK has received one report where alosetron may have been given during pregnancy or at the time of conception. No AEs were reported in this case.

Adverse event cases of special interest

This section reviews post-marketing AE cases that mention a diagnosis and/or outcome of special interest. Diagnoses of special interest are **1) ischemic colitis; 2) mesenteric ischemia, occlusion, or infarction; 3) serious constipation; and 4) complications of constipation**. Outcomes of special interest are **1) intestinal or anorectal surgery,** and **2) death.** These diagnoses and outcomes of interest were identified during review of spontaneously reported AEs from the first marketing cycle (March 2000 to November 2000).

Of the total 127 post-marketing AE cases, 19 (15%) include one or more of these diagnoses and/or outcomes of special interest. [Note: In this document, the diagnoses of special interest are considered mutually exclusive, and cases are not "double-counted" in more than one diagnosis category. If a case could be considered in more than one diagnosis category, the events were evaluated and clinical judgement was used to classify the case in the diagnosis category considered to be the primary event. In contrast, cases are included in all applicable outcome categories and thus may be "double-counted."]

Table 3 lists the 19 AE cases of special interest by Case ID Number (Manufacturer's Control Number) and displays the category(ies) in which each case is included. Individual cases are classified in only one **diagnosis** category but are included in all applicable **outcome** categories**.**

Table 3. Cases of Special Interest

No.	Case ID	Diagnoses of Special Interest				Outcomes of Special Interest		
		Ischemic Colitis (8)	Mesenteric Ischemia, Occlusion, or Infarction (0)	Serious Constipation (0)	Complications of Constipation (8)	Surgery (1 unconfirmed*)		Death (3)
						Intestinal (1 unconfirmed*)	Anorectal (0)	
1	A0394645A				X			
2	A0398212A	X						
3	A0399226A	X						
4	A0400352A	X						
5	A0401595A				X	X (unconfirmed*)		
6	A0405896A				X			
7	A0407541A				X			
8	A0409970A	X						
9	A0423626A				X			
10	A0425537A				X			
11	A0426735A				X			
12	A0428472A							X
13	A0429095A							X
14	A0441187A	X						
15	A0490901A	X						
16	A0492919A				X			
17	A0493979A	X						
18	A0496075A							X
19	A0496949A	X						

* Case A0401595A describes a 60-year-old female who stated that she underwent exploratory laparoscopy for small intestinal obstruction; however the prescribing gastroenterologist was not aware of this event.

Independent Review

At the time Lotronex was re-introduced to the U.S. market in November 2002, GSK established an independent Safety Review Committee (SRC) to provide expert clinical consultation to GSK on AEs of special interest. The SRC independently reviews and adjudicates spontaneous AE reports, as well as AE reports from clinical trials, epidemiological studies, and pharmacogenetics studies that concern AEs of special interest. The SRC has also reviewed and provided input to this summary of post-marketing AEs of special interest. The SRC is comprised of three gastroenterologists and a statistical consultant:

James H. Lewis, M.D.	Georgetown University Hospital, Department of Medicine, Division of Gastroenterology, Washington, DC
JoAnne Wilson, M.D.	Duke University Medical Center, Department of Medicine, Division of Gastroenterology, Durham, NC
Yehuda Ringel, M.D.	University of North Carolina School of Medicine, Division of Digestive Diseases and Nutrition, Chapel Hill, NC
Ralph D'Agostino, Ph.D. (Statistical consultant)	Boston University, Department of Mathematics and Statistics, Boston, MA

Diagnoses of Special Interest

Ischemic Colitis

Summary

Reports of ischemic colitis were identified as cases that included one of the following events or any medical synonym for these events: *ischemic colitis, ischemia of the colon, necrosis of the colon.* GSK has received eight reports of suspected or demonstrated ischemic colitis involving patients who received alosetron after the product was re-introduced. Table 4 displays the key features of the eight reports of ischemic colitis.

Table 4. Reports of Suspected or Demonstrated Ischemic Colitis

Case ID*	Age / Sex	Alosetron Daily Dose	Time to Onset	Diagnostic Tests Performed	Location of Ischemia	Actions Taken, Sequelae, and Outcomes
A0398212A	56 years Female	1 mg	4 weeks	Colonoscopy	Transverse colon adjacent to splenic flexure	Hospitalization, d/c of alosetron, event resolved
A0399226A	31 years Female	1 mg	3-4 weeks	Colonoscopy, Biopsy	Proximal transverse colon	Hospitalization, d/c of alosetron, event resolved
A0400352A	45 years Female	2 mg	53 days	Colonoscopy	Left colon	d/c of alosetron, event resolved
A0409970A	61 years Female	1 mg	13 days	Colonoscopy, Biopsy	Descending colon, sigmoid colon, rectum	Hospitalization, d/c of alosetron, event resolved
A0441187A	65 years Female	1 mg	4 days	Colonoscopy, Biopsy	Sigmoid colon	d/c of alosetron, prednisone therapy, event resolved Pending evaluation for rheumatologic disease due to elevated ESR and CRP
A0490901A	52 years Female	1 mg	16 weeks	Colonoscopy, Biopsy	Descending colon+	d/c of alosetron, event resolved
A0493979A	Unknown Female	1 mg	9 months	None reported	Unknown	d/c of alosetron, event resolved
A0496949A	Unknown Female	Not reported	Not reported	None reported	----	d/c of alosetron, outcome unknown

* Case ID in ***bold italics*** indicates a report received via the Lotronex Patient Follow-up Survey Program (EPI-40255).

ESR – erythrocyte sedimentation rate; CRP – C-reactive protein

+ Report received on January 14, 2004 described location as ascending colon; follow-up report received since data lock described location as descending colon.

All eight reports of ischemic colitis involved female patients ranging in age from 31 to 65 years (where reported). Three patients had received alosetron during the first marketing cycle without AEs (A0398212A, A0409970A, A0441187A).

Six of the eight reports described colonoscopic and/or biopsy findings consistent with possible ischemic colitis. Biopsy results were reported in four cases, two of which specifically noted ischemia (A0409970A, A0441187A). Two reports were not confirmed

by a physician or other healthcare professional and included no diagnostic information (A0493979A, A0496949).

Time to onset of symptoms of ischemic colitis ranged from 4 days to 9 months. Concurrent constipation was not reported in any of the 8 cases.

Two reports described concomitant use of conjugated estrogens (A0398212A, A0441187A).

Three of the patients were hospitalized due to the reported events (A0398212A, A0399226A, A0409970A). No deaths, surgeries, or transfusions were reported among the 8 cases of suspected or demonstrated ischemic colitis.

Case Summaries

Four of the eight cases were initially received from consumers via the Lotronex Patient Follow-Up Survey Program (EPI-40255):

1) Case A0400352A involves a 45-year-old female consumer who stated that she developed abdominal pain and rectal bleeding during treatment with alosetron and was being evaluated for ischemic colitis. Follow-up from the patient's physician provided clinical history and endoscopic data that supported this diagnosis. The patient began treatment with alosetron (2 mg QD) in January 2003 for diarrhea-predominant IBS. Approximately eight weeks later, she developed abdominal pain and rectal bleeding. Flexible sigmoidoscopy revealed ischemic colitis in the left colon. A biopsy was not performed, and the patient was not hospitalized. Stool microbiology was negative for enteric pathogens and cytotoxins. Alosetron was discontinued and the events resolved within several days. The physician stated this event was almost certainly related to alosetron.

2) Case A0409970A involves a 61-year-old female who described the occurrence of ischemic colitis during treatment with alosetron. Follow-up from the patient's physician revealed that the patient had received alosetron in 2000 with marked improvement of her IBS symptoms. She was re-started on alosetron (1 mg QD) in April 2003 and developed abdominal cramping, bloody diarrhea and nausea after two weeks of treatment. The patient was hospitalized for a day, during which time she was treated with hydration and a liquid diet, and underwent a colonoscopy and biopsy. Alsosetron was discontinued. Colonoscopy showed asymmetric superficial ulcerations of the colonic mucosa predominantly involving the descending colon, and sparsely involving the sigmoid colon and rectum. These ulcerative lesions were dispersed within normal mucosa, and no submucosal hemorrhage was noted. Biopsies revealed active colitis with increased acute inflammatory cells within the

lamina propria and epithelium. No crypt abscesses were seen and crypt architecture was not distorted. Changes were suggestive of ischemia although the reporter stated that infection could not be excluded. *C. difficile* and enterohemorrhagic *E.coli* studies were negative. The patient was discharged after one day of hospitalization and her symptoms subsequently resolved.

3) Case A0493979A is a consumer report of intestinal bleeding in a female of unreported age who received alosetron (1 mg QD) for 9 months. The patient was told by her gastroenterologist that the bleeding was due to a "blockage of the blood supply to her large intestine." Treatment with alosetron was discontinued and the events resolved. The patient was not hospitalized. It is not known if she underwent a diagnostic colonoscopy.

4) Case A0496949A involves a female consumer of unknown age who described the occurrence of possible ischemic colitis at an unknown time after starting treatment with alosetron (dose not reported). Treatment with alosetron was discontinued. It is not known if the patient underwent a diagnostic colonoscopy. The outcome of the event is not known.

The remaining 4 cases were spontaneous reports:

5) Case A0398212A is a physician report of a 56-year-old female with diarrhea-predominant IBS. The patient was treated with alosetron for six months in 2000 and did well with no AEs. She was restarted on alosetron (1 mg QD) in January 2003 and after 4 weeks, experienced nausea, vomiting, and rectal bleeding. Alosetron was discontinued. The patient was hospitalized and treated with IV fluids and a liquid diet. Colonoscopy showed ischemic lesions in the transverse colon adjacent to the splenic flexure. No biopsy was performed. The event resolved. This patient received conjugated estrogens through both courses of treatment with alosetron.

6) Case A0399226A is a physician report of a 31-year-old female with diarrhea-predominant IBS. The patient started alosetron (1 mg QD) in February 2003 and 3 weeks later, developed sever abdominal pain, nausea, vomiting, and loose stools. Alosetron was discontinued. Sigmoidoscopy revealed sub-epithelial hemorrhages and erosions at the splenic flexure and diffuse hemorrhagic areas, without ulceration, in the proximal transverse colon. Biopsy showed non-specific reactive changes. The differential diagnosis for the biopsy included "drug injury" and a "non-specific reaction to chronic diarrhea." The patient was hospitalized and the event resolved.

7) Case A0441187A is a physician report of a 65-year-old female with diarrhea-predominant IBS who also had a history of intermittently elevated values for ESR (>120) and C-reactive protein (CRP) and was being evaluated for a possible

rheumatologic syndrome. The patient had received alosetron during the first marketing cycle in 2000, with no adverse effects. She saw her gastroenterologist in July 2003 for abdominal pain and diarrhea, and she was started on alosetron (1 mg QD) in October 2003. Four days after starting treatment, she complained of lower abdominal pain, bloody stools, and constipation, which led her to discontinue treatment. She consulted her gastroenterologist one month later for ongoing abdominal pain, constipation, and weight loss. A colonoscopy revealed patchy erythema in the sigmoid colon, and histology was indicative of chronic ischemic colitis. At the time of this biopsy, her ESR and CRP were extremely high, which led her physician to commence empiric treatment with prednisone (60 mg QD). Her symptoms resolved within several weeks and she was continued on low dose prednisone (10mg QD). The gastroenterologist believed that these events were most likely related to an underlying vasculitis that may have been exacerbated by the patient's use of alosetron.

8) Case A0490901A is a physician report of a 52-year-old female who received alosetron (1mg QD) for approximately 4 months, at which time she developed bloody diarrhea, nausea, and vomiting. Alosetron was discontinued. A biopsy performed 4 days after these symptoms developed revealed a "patch" in the descending colon that was "non-specific." The physician felt that this episode was consistent with mild ischemic colitis. The patient was not hospitalized and the events resolved.

Mesenteric Ischemia, Occlusion, or Infarction

To identify cases of mesenteric ischemia, occlusion, or infarction, the GSK safety database is searched using broad groups of gastrointestinal event terms in MedDRA. From the cases retrieved, all cases with terms possibly representing mesenteric ischemia, occlusion, or infarction are selected.

GSK has received no reports of mesenteric ischemia, occlusion, or infarction involving patients prescribed alosetron after the re-introduction of the product.

Serious Constipation

Cases of serious constipation are identified by searching the GSK safety database for all cases that were assessed as "serious" under the provisions of 21 CFR 314.80(a) or were considered medically serious by GSK. From these serious cases, cases with a reported event of constipation or related term are identified, then individually reviewed to determine if constipation was the event that led to the assessment of "serious." This last step is necessary because seriousness is coded at a case level, even though multiple terms are extracted and coded from the reporter's narrative, many of which may not be serious under the provisions of 21 CFR 314.80(a). [For example, the search using these terms may have revealed a case of a hip fracture leading to hospitalization and incidentally, the

reporter mentioned that the patient had constipation in the hospital. In this example, the fracture was the event causing the case to be designated as "serious" and not the constipation, and this case would not be included in the diagnosis category of serious constipation.]

GSK has received no reports of serious constipation involving patients prescribed alosetron after the re-introduction of the product.

Complications of Constipation

Summary

Reports of complications of constipation were identified as cases that included events such as the following: *obstruction, perforation, intestinal ulceration, toxic megacolon, ileus*, or *fecal impaction resulting in hospitalization or emergency room visit*.

GSK has received eight reports of events considered complications of constipation involving patients prescribed alosetron after the re-introduction of the product. These eight reports include three cases of fecal impaction, three cases of intestinal obstruction, one case of ileus, and one case of intestinal ulceration. Table 5 displays the key features of these eight reports.

Table 5. Reports of Complications of Constipation

Case ID*	Age / Sex	Alosetron Daily Dose	Time to Onset	Event	Actions Taken, Sequelae, and Outcomes
A0394645A	59 years Female	1 mg	5 days	Intestinal obstruction	Hospitalization, d/c of alosetron, event resolved
A0401595A	60 years Female	Not reported	Not reported	Small intestine obstruction	Exploratory laparoscopy (per patient, not confirmed by physician), outcome unknown
A0405896A	82 years Female	1 mg	1 month	Ileus	Hospitalized, alosetron continued, event resolved.
A0407541A	Unknown Female	Not reported	Not reported	Fecal impaction	Emergency room (treatment not reported), outcome unknown
A0423626A	49 years Female	4 mg	~ 4 months	Fecal impaction	Emergency room (magnesium citrate), d/c of alosetron, event resolved
A0425537A	Unknown Female	Not reported	1 week	Intestinal obstruction	Hospitalized, d/c of alosetron, event resolved
A0426735	Unknown Female	Not reported	Not reported	Ulcerated colon (per patient's report of colonoscopy result)	Treated with prednisone, d/c of alosetron, event resolved
A0492919A	Unknown Female	1 mg	4 months	Fecal impaction	Emergency room (treatment not reported), event resolved, alosetron d/c one month later

* Case ID in ***bold italics*** indicates a report received via the Lotronex Patient Follow-up Survey Program (EPI-40255).

All eight reports involved female patients ranging in age from 49 to 82 years (where reported). Three patients had received alosetron during the first marketing cycle without AEs (A0394645A, A0401595A, A0405896A).

Five of the eight reports were reported only by the consumer and include no confirmation or information from a physician or other healthcare professional (A0401595A, A0407541A, A0425537A, A0426735A, A0492919A).

Time to onset of symptoms ranged from 5 days to 4 months (where reported).

Three of the patients were reported as being hospitalized due to the reported events and three patients reported visiting the emergency room for treatment. No deaths, confirmed surgeries, or transfusions were reported among the eight cases of complications of constipation.

Case Summaries

Seven of the eight cases were initially received from consumers via the Lotronex Patient Follow-Up Survey Program (EPI-40255):

1) Case A0394645A describes a 59-year-old female who reported partial intestinal obstruction. On follow-up, the prescribing physician reported that the patient, whose past medical history includes diarrhea-predominant IBS and hypothyroidism, received alosetron (1mg QD) for several months during the initial marketing period, during which time her symptoms improved. She was restarted on alosetron (1mg QD) in January of 2003. After five days she experienced severe abdominal distension, bloating, and persistent diarrhea. She was hospitalized for three days and alosetron was discontinued. Serum potassium levels decreased at the time of admission (3.0 mEq/L) which the physician attributed to persistent diarrhea. Abdominal x- rays on admission showed early, incomplete small bowel obstruction; barium enema performed during the hospitalization showed a redundant colon with retained feces. The physician felt that the AEs were attributable to alosetron use and elected not to re-start alosetron. He also stated that the low potassium level may have contributed to the development of this event. The patient's symptoms rapidly improved during hospitalization and she was discharged.

2) Case A0401595A involves a 60-year-old female who stated that she underwent exploratory laparoscopy for small intestinal obstruction; however the prescribing gastroenterologist was not aware of this event.

3) Case A0405896A involves an 82-year-old female with IBS who reported constipation and subsequent hospitalization. On follow-up, her physician reported that the patient has chronic lymphocytic leukemia and breast cancer. She received alosetron (1mg BID) during the first marketing cycle and did well. She was re-started on alosetron (1mg QD) in March 2003 and was hospitalized approximately one month later for possible mild ileus. The physician believed that the ileus was secondary to the patient's underlying malignancies and to a new pleural effusion that was diagnosed during the hospitalization. The patient's symptoms resolved and she remained on alosetron (1mg QD).

4) Case A0407541A describes a female of unreported age who stated that she developed a "bad blockage" and that she went to an emergency room for treatment. No other information is available at this time.

5) Case A0425537A involves a female of unreported age who reported the occurrence of diarrhea and intestinal obstruction after approximately one week of alosetron treatment. The patient was hospitalized, alosetron was discontinued, and the events resolved.

6) Case A0426735 describes a female of unreported age who received alosetron for an unspecified period of time and for an unknown indication. The patient stated that she underwent a colonoscopy and was found to have an ulcerated colon. There was no history of constipation, and the event resolved with prednisone. Although this event may represent an inflammatory bowel lesion, rather than a complication of constipation, it is included in this section in accordance with the approval letter of June 2002, which stipulates that GSK consider all cases of intestinal ulceration under the category of complications of constipation.

7) Case A0492919A is a consumer report describing the occurrence of fecal impaction in a female of unreported age after 4 months of treatment with alosetron (1 mg QD). The patient stated that she developed symptoms of "bowel obstruction" where she felt like "she was having a baby." The patient went to the emergency room but did not state what treatment she received. She was not hospitalized. The event resolved and she had no further problems. Alosetron was discontinued after a total of 5 months of treatment. This report has not been medically confirmed.

The eighth case was a spontaneous report:

8) Case A0423626A was received from a nurse and described the occurrence of fecal impaction in a 49 year old female patient with diarrhea-predominant IBS. The patient reportedly received alosetron (2 mg BID) and after approximately four months, developed worsening diarrhea, abdominal pain, and nausea. She was evaluated in the emergency room and fecal impaction was diagnosed via CT scan. Alosetron was discontinued. The patient was treated with cathartics, and the impaction resolved within several days. The patient had taken numerous constipating medications including cholestyramine, loperamide, and hyoscyamine; however, it was not certain that she was receiving them while taking alosetron.

Outcomes of Special Interest

Surgery

There has been one unconfirmed report of surgery. Case A0401595A involves a 60-year-old female who stated that she underwent exploratory laparoscopy for small intestinal obstruction; however, when contacted by GSK, the prescribing gastroenterologist was not aware of the event or the procedure.

Death

GSK has received three post-marketing reports of death involving patients prescribed Lotronex after re-introduction of the product.
Two deaths were reported by family members of patients enrolled in the Lotronex Patient Follow-up Survey Program (EPI-40255). GSK became aware of these deaths during the course of routine follow-up of the survey participants. One death occurred in a 67-year-old female whose husband stated that the cause of death was multiple myeloma (A0428472A). The second death involved a male patient of unreported age whose mother stated that he had died from complications of acquired immunodeficiency syndrome (AIDS) (A0429095A).

The third death was reported by a physician (A0496075A). This case involved a 58-year-old female with multiple medical problems including obesity, fatty liver, hypertension, hyperthyroidism, and IBS. The physician reported that approximately seven months after starting treatment with alosetron, the patient suddenly stopped breathing and became unresponsive. The patient died in the emergency room. The physician suspects the cause of death to be pulmonary embolism; however, no autopsy was performed.

Summary

1. Alosetron was first marketed in the U.S. from March 13, 2000 to November 28, 2000 and was withdrawn following reports of serious gastrointestinal events. During this time, approximately 534,000 prescriptions were dispensed to approximately 275,000 individual patients. The product was re-introduced to the U.S. market on November 20, 2002 with a narrowed indication and a risk management program. From November 20, 2002 to February 6, 2004, approximately 34,000 prescriptions were dispensed to approximately 10,000 individual patients.
2. The conditions for reporting AEs following product re-introduction are different from those during marketing in 2000. One key difference is that physicians enrolled in the Prescribing Program for Lotronex (PPL) agree to report all serious AEs as a condition of participation. The second difference is that GSK is receiving AEs from patients participating in the ongoing Lotronex Patient Follow-Up Survey Program (EPI-40255). This survey is not designed to collect safety information or AEs; however,

survey participants occasionally make reference to AEs, which are then reported by GSK to FDA in the same fashion as spontaneously reported AEs.

3. As of February 6, 2004, a total of 127 post-marketing AE cases involving patients treated with alosetron **after** re-introduction of the product had been received by GSK.

   - Twenty-nine (23%) of the 127 reports were received via the Lotronex Patient Follow-Up Survey Program (EPI-40255). Thirty-seven (29%) of the 127 cases were considered "serious" under the provisions of 21 CFR 314.80(a) and/or were considered medically serious by GSK. Approximately 48% of all reported AEs involved the gastrointestinal system organ class. Four gastrointestinal diagnoses of special interest have been closely monitored since the re-introduction of alosetron: (1) ischemic colitis; (2) mesenteric ischemia, occlusion, or infarction; (3) serious constipation; and (4) complications of constipation.
   - *Ischemic colitis.* GSK has received eight post-marketing reports of suspected or demonstrated ischemic colitis involving patients prescribed alosetron after re-introduction of the product. Six of these patients underwent colonoscopy, and two had biopsies that confirmed the diagnosis. Three patients of these eight patients were briefly hospitalized, none required surgery or transfusion.
   - *Mesenteric ischemia, occlusion, or infarction.* No post-marketing reports of mesenteric ischemia, occlusion, or infarction have been received since re-introduction of alosetron.
   - *Serious constipation*. GSK has received no post-marketing reports of serious constipation involving patients prescribed alosetron after the re-introduction of the product.
   - *Complications of constipation:* GSK has received eight post-marketing reports of possible complications of constipation involving patients prescribed alosetron after re-introduction of the product. This includes a report (A401595A) from the Lotronex Patient Follow-Up Survey Program in which the consumer stated she underwent "laparoscopy" for a "small bowel obstruction." The prescribing physician said that he was not aware that the patient had undergone any surgical procedures.

4. There have been three post-marketing reports of death involving patients prescribed alosetron after re-introduction of the product. Two of these reports were received from family members during routine follow-up of patients enrolled in the Lotronex Patient Follow-up Survey Program. Causes of death for these three patients were reported as (1) complications of AIDS, (2) multiple myeloma, and (3) respiratory arrest thought to be due to a pulmonary embolism. None of the deaths were believed to be related to the use of alosetron.

5. The AE reports for diagnoses of special interest suggest that patients and physicians took appropriate and prompt action to discontinue Lotronex in the setting of rectal bleeding, worsening pain, constipation, or symptoms of obstruction.
6. The AE reports for diagnoses of special interest also suggest that when the events did occur, they generally resolved without sequelae. This is in contrast to the first marketing cycle, where serious gastrointestinal events sometimes resulting in intestinal surgeries and in rare cases, deaths, were reported.

Conclusions:

Review of the post-marketing data did not identify any new safety issues. Considering the relatively low patient exposure since re-introduction and the low number of AEs of special interest reported, caution should be exercised in comparing the safety profiles from the two marketing cycles. However, based on the available information, it appears that AEs of special interest have been similar in nature, but generally less severe, than those reported prior to adoption of the Prescribing Program for LOTRONEX and other restricted conditions of use. These reports also suggest that AEs of special interest are being managed effectively.

Section III: Emerging Issues

Section III: Emerging Issues

Implementation of the RMP for Lotronex, as agreed with FDA, has been successful. However, the apparent impact of the RMP on physician and patient usage indicates that elements of the RMP itself may be posing an inappropriate/unintended barrier to product use. One year after product reintroduction, the number of physicians enrolled in the Prescribing Program for Lotronex (PPL) is approximately 10% of the number of physicians (50,000) prescribing Lotronex in the initial marketing period. Even more disconcerting is the fact that of the physicians enrolled in the PPL, less than one in four have yet to prescribe and of the practitioners that have prescribed only half have done so more than five times since re-introduction of the product. Initial estimates of the severe d-IBS patient population in the U.S. range from 100,000-185,000 yet only 10,000 patients have been prescribed Lotronex over the initial 12 months following product re-introduction. These observations point to three key issues with regards to the RMP:

1. Impact of the RMP for Lotronex on the Physician
2. Impact of the RMP for Lotronex on the Patient
3. Impact of Current Prescribing Rate on Evaluation of the RMP

In the ensuing sections these issues will be discussed in detail.

- **Impact of the RMP for Lotronex on the Physician**

A goal of the RMP for Lotronex is the enrollment of qualified physicians in a physician prescribing program. This is accomplished through the enrollment of physicians in the PPL. As part of that process, the practitioner is required to sign the Physician Attestation Form and certify that he/she possesses certain qualifications including the ability to diagnose and manage IBS, ischemic colitis, constipation and complications of constipation. Physician feedback, including the formal research being conducted with practitioners by GSK, indicates that many physicians see this as an affront to their training and an unnecessary duplication of the activities subsumed in the physician licensure process.

Furthermore, there is a perception -whether accurate or not- that the attestation process described in the preceding paragraph constitutes a unique transfer of product liability to the prescribing physician. This perception could be the basis of the apparent practice pattern arising from the Patient Follow-Up Survey for Lotronex. Current data from the survey indicate that approximately 80% of the survey respondents receiving Lotronex have all three criteria (frequent and severe abdominal pain/discomfort, frequent bowel urgency or fecal incontinence disability or restriction of daily activities due to IBS) defining severe diarrhea predominant IBS where only one is required. It is possible that liability concerns - again, whether or not they are well-founded - are leading physicians

to reserve treatment with Lotronex to patients at the extreme end of the severity spectrum.

Our research and interactions with prescribers has exposed another problematic aspect of the RMP for Lotronex that was not considered at the time the program was developed, namely, the discordance between physician requirements under the current RMP and the time constraints of the typical office practice paradigm. To prescribe Lotronex, the practitioner must do the following:

- Enroll in the PPL for Lotronex;
- Sign the Attestation Form;
- Educate patients on the benefits and risks of treatment with Lotronex, provide them with the Medication Guide, instruct them to read it, and encourage them to ask questions;
- Discuss the Patient-Physician Agreement form with the patient, obtain the patient's signature on the form, sign it themselves, place the original signed form in the patient's medical record, and give a copy to the patient;
- Affix program stickers provided as part of the PPL for Lotronex. to <u>all</u> prescriptions for Lotronex. There are no refills. Each dispensing of Lotronex requires a physician signed prescription with the sticker affixed;
- Re-assess the patient each month before writing a new prescription.

The time required for the physician to complete these activities is disproportionate compared to the time spent in prescribing other medications (i.e., of similar or less severe risk profiles) and to the time spent explaining and obtaining patient consent to invasive procedures. This apparent mismatch is proving to be a disincentive to product use. Alternatives designed to streamline the process are required if Lotronex is to be available to a broader segment of the severe diarrhea predominant IBS patient population.

- **Impact of the RMP for Lotronex on the Patient**

Product labeling supporting the reintroduction of Lotronex to the marketplace is very heavily oriented towards providing information regarding the risks and potential dire consequences of product use with relatively little information regarding potential benefit. Before a patient can receive Lotronex he/she must read the Medication Guide discuss the risks and benefits of treatment with Lotronex with their physician and read, discuss and sign the Patient-Physician Agreement. According to feedback that we are receiving from the field, the combination of the concern raised by the information contained in the patient directed labeling plus the unusual requirement for the patient to sign an agreement prior to receiving a prescription is causing patients to refuse treatment. Significant support for the negative impact of the patient directed product labeling for Lotronex on patient use can be found in the current clinical trials program. In these studies, based on

subject review of information identical to that contained in the Medication Guide, 28% of all patients offered the opportunity to participate have refused to consent and have stated that they are afraid to take Lotronex. This is even more disconcerting when one understands that the physicians considered these patients to be appropriate candidates for treatment with Lotronex prior to being approached regarding study participation.

- **Impact of Current Prescribing Rate on Evaluation of the RMP**

The longitudinal claims-based observational studies form a significant component of the program evaluation requirement for the RMP for Lotronex and consist of four databases covering approximately 8.5 million lives. Achieving the objectives of this series of longitudinal claims-based observational studies is entirely dependent upon the amount of product prescribed. Far too few users of Lotronex have been identified from the cohort of patients that have received Lotronex to date. To provide the basis for a meaningful evaluation of data from these studies, approximately 2,000 patients will need to be identified. To achieve this approximately 155,000 patients will need to be treated with Lotronex.

The FDA has been receiving quarterly progress updates from GSK on the implementation and impact of the RMP for Lotronex. In the context of these updates the FDA has been made aware of the issues that have been presented in the preceding paragraphs. Our goal is to work with the FDA to modify the RMP for Lotronex to improve product access for appropriate physicians and patients while continuing to effectively manage risk.

Section IV: Discussion and Conclusions

Section IV: Discussion and Conclusions

The Risk Management Program (RMP) for Lotronex consists of a complex series of interrelated tools, interventions, and evaluations that seeks to ensure, to the extent possible, that Lotronex is made available to appropriate and informed patients identified and managed appropriately by knowledgeable physicians.

The concept of risk management, as an integral part of product pharmacovigilance, is evolving. The RMP for Lotronex was designed according to contemporary norms of good medical governance and product stewardship and this was done in the absence of a template or of guidance based on prior demonstrated success. Therefore, it is instrumental that the effectiveness of the program be evaluated on an ongoing manner and revisions be implemented, as appropriate.

A summary of the experience with implementation of the RMP from product re-introduction in November 2002 through December 2003 (February 2004 for post-marketing surveillance) has been presented in this Briefing Document. Overall the implementation of all of the elements of the RMP has occurred successfully and in a timely manner. Since the re-introduction of Lotronex, data have been collected from various sources and interrogated and demonstrates great strengths in the program as well as notable weaknesses.

To date, approximately 80% of prescriptions, from month to month, have been written by physicians enrolled in the Prescribing Program for Lotronex (PPL). This represents a high level of participation. Moreover, follow-up of prescribing non-enrollees has resulted in a significant increase in compliance with these physicians who either enroll in the PPL or cease to prescribe. As expected, gastroenterologists write most of the prescriptions and almost all of the gastroenterologists are enrolled in the PPL. Importantly, approximately 40% of prescriptions are written by primary care physicians (PCP) and most of these physicians are also enrolled in the PPL. This supports the proposition that much IBS care is provided by knowledgeable and experienced PCPs who may well practice in areas under-served by gastroenterologists. Very few prescriptions for Lotronex have been written by other specialties.

However, there are serious concerns that access to the medication by appropriate patients has been significantly limited as a result of inappropriate and unintended barriers imposed by certain aspects of the PPL in particular, and the RMP in general. Far fewer physicians have enrolled than anticipated, those enrolled prescribe very little and the 10,000 patients treated to date represents a small fraction of the population of women with severe D-IBS who have failed conventional therapy. In other words, a significant unmet medical need that could potentially be addressed by Lotronex remains unfulfilled.

From the perspective of physicians, having to comply with the requirements of the RMP the overriding opinion gained from interviews and focus groups has been that the RMP is insulting to their professional integrity, excessively time-consuming and out of proportion to practice norms. Additionally, there is the common perception - whether well founded or not - that unique product liability has been shifted to the practitioner. It would appear that these considerations are leading many physicians not to prescribe Lotronex at all while the small number of physicians that do, appear to reserve treatment to patients at the extreme end of the severity spectrum. This is borne out by data from the Patient Survey indicating that approximately 80% of the eligible patients fulfill all three severity criteria, when only one is needed to define severe D-IBS and qualify the patient for treatment with Lotronex.

Product labeling may well be contributing to an unintended barrier to appropriate access of the product. Labeling focuses almost entirely on risks and communicates that risk in an unbalanced manner that tends to frighten rather than inform the patient. In addition, by minimizing information regarding potential benefits associated with Lotronex, the critical dialogue between a patient and her physician as to whether the benefits of treatment outweigh the risks is severely compromised.

Educating patients, physicians and pharmacists on IBS, the benefits and risks of Lotronex therapy, the elements of the RMP and how to be in compliance with the PPL is an ongoing multi-modal endeavor. As described in this Briefing Document, a large number of physicians and pharmacists have been targeted. Significant focus is placed on identifying and managing appropriate patients as well as providing guidance on how to recognize, diagnose and manage the predominant safety concerns, complications of constipation, and ischemic colitis. Success is measured in terms of the high degree of compliance with the elements of the PPL demonstrated by the PPL evaluation study, the Patient Survey, and from review of the safety data suggesting a decrease in the severity and sequelae of reported adverse events secondary, in part, to appropriate management.

The Patient Survey provides on-going real time data. Participation is voluntary and there has been a strong response rate and a high degree of compliance maintained over time. Less than 10% of the survey respondents are men and most patients' report using a dose of Lotronex of 1mg QD, initially.

The Epidemiologic Program for the Study of the Safety and Utilization of Lotronex in the US is dependent on prescribing volume. A disappointing consequence of the low prescribing rate is that there is little useful information to be gained from this program at this time.

Review of all post-marketing AE and SAE reports (including events of special interest) received from the time of re-introduction of the product and implementation of the risk management plan on November 20, 2002 up to February 6, 2004 indicates no new safety signals. Conditions for reporting adverse events differ from the usual (and previous) approach and are unique to Lotronex. One key difference is that physicians enrolled in the PPL agree to report all serious adverse events as a condition of participation. The second difference is that unsolicited reports of adverse events have been received from patients through participation in the Patient Survey. Twenty-three percent (23%) of all AEs has been reported in this way.

Events of special interest were pre-specified based on review of spontaneously reported AEs from the first marketing cycle (March 2000 to November 2000). Diagnoses of special interest are ischemic colitis, mesenteric ischemia, occlusion, or infarction, serious constipation and complications of constipation. Outcomes of special interest are intestinal or anorectal surgery**,** and death**.**

To date, since the re-introduction of Lotronex, approximately 35,000 prescriptions for Lotronex have been written for 10,000 patients. Eight post-marketing reports of suspected or demonstrated ischemic colitis have been received. Six of these patients underwent colonoscopy, and two had biopsies that supported the diagnosis. Three of these eight patients were briefly hospitalized; none required surgery or blood transfusion. No reports of mesenteric ischemia, occlusion, or infarction have been received and similarly, there have been no reports of serious constipation. Eight reports of possible complications of constipation were received. This includes one consumer report of "laparoscopy" for a "small bowel obstruction " which was not confirmed by the patient's physician. The remaining seven cases include three cases of fecal impaction, two cases of intestinal obstruction, one case of ileus, and one case of intestinal ulceration. Five of the eight cases were reported only by the consumer and include no confirmation or information from a physician or other healthcare professional. Three of the patients were reported as being hospitalized and three patients reported visiting the emergency room for treatment. No confirmed surgeries and no transfusions or deaths were reported among the eight cases of complications of constipation. Review of individual adverse event reports for diagnoses of special interest suggest that patients and physicians took prompt and appropriate action.

Three post-marketing reports of death were reported to GSK. Two of these reports were received from family members during routine survey follow-up of patients enrolled in the Lotronex Patient Follow-up Survey Program. Causes of death for these two patients were reported as complications of AIDS and multiple myeloma. The cause of death for the third case was reported as respiratory arrest thought to be due to a pulmonary embolism. None of the deaths were believed to be related to the use of Lotronex. Since ongoing

clinical trials are blinded to treatment assignment, safety data from these trials have not undergone an un-blinded evaluation for this update of the RMP; however, a blinded review of serious adverse events and non-serious events of special interest has not revealed a need to alter the current clinical trial program.

Assessment of the safety data accrued since the reintroduction of Lotronex has not identified any new safety issues. The number of patients exposed to Lotronex is substantially smaller since the reintroduction of the product under the RMP than it was during the first marketing cycle. In addition, as described above, the approach applied to the collection of adverse events is different. Nevertheless, within this smaller sample, outcomes of adverse events have been generally less severe than those reported prior to the reintroduction and suggests that AEs of special interest are being managed effectively. These conclusions represent the consensus view of GSK and the independent Safety Review Committee established by GSK at the time Lotronex was re-introduced to the U.S. market.

In summary, IBS represents a significant unmet medical need and is associated with significant personal cost to patients in terms of their well being as well as enormous economic costs to the healthcare system. Among available treatments, only Lotronex has been proven to improve the most bothersome symptoms of severe diarrhea-predominant IBS in women in adequate and well-controlled trials. For many patients, the burden of illness is not alleviated with conventional therapy resulting in a significant negative impact on daily functional status and quality of life. In addition, conventional therapy in IBS is often dependent on unapproved approaches with undefined risk-benefit profiles. Under the current Risk Management Plan, the potential risks associated with Lotronex use have been effectively managed. Thus, for women with severe d-IBS, Lotronex is an appropriate choice, given the magnitude of treatment benefits in the setting of a significant burden of illness with no effective alternatives. In other words, the benefit to risk balance is favorable.

The primary concern at present relates to the low rate of product prescribing given our understanding of the target population size. This may reflect unintended barriers to prescription to the extent that appropriate and needy patients are being under served. Alternatives designed to redirect or remove some of the unintended barriers from the physician and from the patient are required if Lotronex is to address the significant unmet medical need of appropriate women with severe diarrhea predominant IBS.

Our goal is to work with the FDA to modify the RMP for Lotronex to improve product access for appropriate physicians and patients while continuing to effectively manage risk.