MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PID NUMBER: #D000674

DATE: November 16 2000 (Redacted Version)

TO: Lilia Talarico, M.D., Director
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

FROM:
- Kathleen Uhl, M.D., Acting Division Director
- Zili Li, M.D., M.P.H., Medical Epidemiologist
- Ann Corken Mackey, R.Ph., M.P.H., Safety Evaluator
Division of Drug Risk Evaluation II (DDRE II), OPDRA, HFD-440
- Paul Stolley, M.D., M.P.H., Epidemiology Consultant
OPDRA, HFD-400

SUBJECT: NDA 21-107: Lotronex (alosetron) Safety & Risk Management Summary

1. EXECUTIVE SUMMARY

DDRE2 in OPDRA has prepared two separate presentations regarding the data on the risk of Lotronex (alosetron), indicated for the treatment of women with diarrhea-predominant irritable bowel syndrome (IBS). On November 7, 2000, OPDRA made a presentation to Dr. Janet Woodcock, CDER Center Director, on the adverse event reports received since the approval of Lotronex, on February 8, 2000, and on the risk of Lotronex. OPDRA prepared for a presentation to be given during the face-to-face meeting with the sponsor, GlaxoWellcome, on November 13, 2000. However, due to time constraints at this meeting, no OPDRA presentation was made. The modified data prepared for this November 13, 2000 meeting are attached to this document (Attachment 1). The data have been modified to include all reports received up to November 10, 2000, including several new reports, and reconciling duplicate reports that were received as both direct and sponsor reports.

The salient details of the data from both presentations will be discussed in this memo. In addition, we will state why we do not accept the sponsor's conclusions that all the severe adverse events for Lotronex are directly related to constipation and that a risk management strategy targeting constipation will prevent the serious outcomes seen with the use of Lotronex. It may be that preventing Lotronex-induced constipation will reduce the serious complications of prolonged or severe constipation, and that would be desirable. It has not been proved, however, that preventing constipation will also prevent ischemic colitis, occlusive or non-occlusive, "primary" or "secondary".

It is our interpretation of the cases in AERS that Lotronex is associated with colonic mucosal ischemia and sometimes transmural infarction as well as severe complications of constipation. Some of these cases of colon ischemia may be the result of severe constipation leading to subsequent pressure-related colon ischemia, necrosis, or perforation resulting in colon resection and/or death. Other cases of colon ischemia are not clearly linked to constipation but occur in relatively young women (age < 65 years) with or without bloody diarrhea. Any risk management program aimed at controlling the risk of Lotronex therapy via identification and management of constipation **only** will not be successful. Constipation has **not** been identified in all cases that resulted in hospitalization, ~~blood transfusion~~, surgery, and death. Also, the sponsor has not identified a subset of women who will respond to Lotronex therapy safely. Therefore, a risk management plan cannot be successful that will eliminate deaths, colectomies, ischemic colitis, and complications of treatment that were never seen previously in the management of IBS.

2. BACKGROUND

Lotronex as a therapy for IBS, represents a drug with a new mechanism of action, with modest efficacy for only women with the diarrhea-predominant form of IBS. Therapeutic gain in comparison to placebo was modest.

Ischemic colitis was seen in 3 patients of the 921 treated with Lotronex in the Phase 3 studies for Lotronex. One more patient in an ongoing study was reported just before the November 16, 1999 Advisory Committee meeting. Constipation was the major reason for discontinuation and drop outs in the Phase 3 studies. Constipation was dose-related and the most frequent reason for withdrawal. About one-third of women taking the recommended dose of 1mg twice daily will develop symptomatic constipation and about 10% will have to discontinue the drug permanently.

In the Medical Team Leader Secondary Review by Dr. Hugo Gallo-Torres, November 17, 1999, Table 15 compares the key findings in the Lotronex-treated patients developing colitis in the randomized clinical trials (NDA dataset). Four cases were identified. Interestingly, all 4 patients were under age 65 (ages: 33, 48, 41, 61). One of these 4 had constipation symptoms and the remaining 3 had diarrhea symptoms, and all 4 had rectal bleeding. These 4 cases represent the clearest association between Lotronex use and the development of ischemic colitis. There was no argument that these cases were confounded or represented some distinct classification of "primary" vs. "secondary" ischemia.

3. METHODS

OPDRA reviewed all adverse event reports received for Lotronex as of November 10, 2000, after 36 weeks of marketing. Those with any mention of death, mesenteric vasculopathy, ischemic colitis, or severe constipation were entered into an ACCESS database to capture key details and allow for a surveillance strategy. Data sources included cases provided via the Adverse Event Reporting System (AERS) at FDA and drug utilization data provided under contract by IMS Health. Cases were excluded if the key event could not be verified by FDA.

Case definitions for two of the serious outcomes used in this review are:

(1) **Ischemic Colitis:** A diagnosis of ischemic colitis, ischemic changes or necrosis of colon based on any or a combination of the following: (1) clinical judgement, (2) endoscopic examination or (3) pathology report;

(2) Severe Constipation: constipation or suspected constipation that led to ER visit, hospitalization, or complications, including but not limited to, fecal impaction, bowel obstruction, necrosis or rupture.

(3) In OPDRA's analysis, those surgical cases classified as ischemic colitis had to have clinical diagnosis or histologic evidence of ischemic colitis to meet that classification.

Data and cases were compared between those presented at the GI Advisory Committee meeting on June 27, 2000 (through June 1, 2000) and those known as of November 10, 2000.

4. RESULTS

As of November 10, 2000, there were 49 cases of ischemic colitis, 21 cases of severe constipation, 3 cases of mesenteric vasculopathy, and 5 cases of death, of which 3 are "probable". This is a sharp increase from the number of cases presented at the June 27, 2000 GI AC meeting. As of that date there were 5 cases of ischemic colitis, 5 cases of severe constipation, no cases of mesenteric vasculopathy, and no cases of death. The cumulative number of prescriptions for Lotronex dispensed between March and October 2000 was 435,000 (data presented by GlaxoWellcome to HFD-180 on October 25, 2000), leading to a reporting rate of 113 cases of reported ischemic colitis per million prescriptions and 48 cases of reported severe constipation per million prescriptions.

The severity of the Lotronex-associated adverse events requires specific comment. Of the 49 cases of ischemic colitis, 2 had visits to the ER without hospitalization, however, 30 (65%) required hospitalization, 5 (11%) required surgery for an obstructed, necrotic, or ruptured bowel, and 2 died. Of the 21 cases of severe constipation, 2 had visits to the ER without hospitalization, however, 14 (67%) required hospitalization, 5 (24%) required surgery for an obstructed, necrotic, or ruptured bowel, 6 (29%) had a bowel obstruction that did not require surgery, and 1 died. A full representation of all cases is depicted in the Attachments (Tables 1-1, 1-2, and 5).

Of the 49 cases of ischemic colitis, 38 (78%) had either histological, endoscopic, or radiologic evidence of ischemic colitis, ischemic change, or necrosis (Table 1-3). Fourteen cases (29%) had both histological and endoscopic evidence. Eight (16%) had only endoscopic evidence; 13 (27%) had only histological evidence; 3 (6%) had only radiological evidence.

The severity of the cases as of the June 27, 2000 GI AC meeting, demonstrate that no cases required transfusion, no cases of ischemic colitis required surgery, but 2 cases of severe constipation required surgery (Table 2-1). As of November 10, 2000, 2 cases required red blood cell transfusion (one each for ischemic colitis and severe constipation), 5 cases of ischemic colitis required surgery, and 5 cases of severe constipation required surgery. Additionally, there were 2 deaths in the ischemic colitis and 1 death in the severe constipation groups. We have received a total of 5 reports of deaths in Lotronex users: we have enough data on 3 to rate them as "probable"; 1 is tied up in litigation and we cannot get any more information; and 1 is "unlikely". Much has changed since the June 27, 2000 AC meeting.

Three complicated cases of mesenteric vasculopathy were reported in conjunction with Lotronex use. These cases are "confounded" but represent true use of a drug product once approved. One patient (Case #68) had a history of a DVT and had a Factor V Leiden hypercoagulable state. Case #66 had a pre-existing history of ischemic bowel, had discontinued Lotronex for an uncertain amount of time prior to developing a superior mesenteric artery thrombosis and died. Case #67 had a presumptive diagnosis of mesenteric ischemia/thrombosis with a normal CT scan and colonoscopy 3 days later.

5. GlaxoWellcome's arguments concerning the cases

In the meeting with GlaxoWellcome on November 13, 2000, the sponsor presented a rebuttal of all cases reported on Lotronex associated with mesenteric vasculopathy, death, and surgery. An argument that GlaxoWellcome advanced was to differentiate between "primary" and "secondary" ischemic colitis or colon ischemia. Their consultant, Dr. [redacted] of [redacted] Medical Center, indicated that 70% of cases are usually transient, reversible, spontaneous, do not recur and are classified as primary ischemic colitis. Dr [redacted] indicated that 30% of cases of colon ischemia are due to secondary ischemia that is irreversible and the result of mechanical issues like stricture, toxic dilation of the colon, and distention. Their contention was that all the cases of "ischemia" identified by FDA were of the secondary ischemia variety and could therefore be eliminated via proper identification and management of constipation. Their contention was that none of the cases the FDA classified as ischemic colitis were of the primary ischemic colitis variety. They do not agree that primary ischemic colitis has led to death or sequelae.

It is irrelevant whether the ischemia is classified as "primary" or "secondary" and this distinction is arbitrary. It is more likely that ischemic colitis represents a spectrum of severity rather than two separate disorders. If secondary ischemia occurs only in the situation where there is mechanical obstruction, if the obstruction is severe enough and of long enough duration, the bowel will dilate, the wall will thin, necrosis, and perforation will result. Colon ischemia, as defined by their consultant, occurs most commonly in the elderly who are otherwise healthy, is not painful, is accompanied by rectal bleeding and bloody diarrhea. It is not true that all the cases of ischemic colitis identified by FDA were "secondary" (using Dr. [redacted] terminology). The first three cases seen in the NDA studies were all of the relatively mild, reversible, "primary" type.

In the surgical bowel resection cases, 7 involved resection of the sigmoid colon only, 1 involved the sigmoid and left colon, 1 involved the right colon, and 1 involved the right and transverse colon.

Of the 3 cases (Cases #64, 21, & 43) that resulted in death (Table 5), 2 had presenting symptoms of abdominal pain, only one had constipation, and none had bloody diarrhea. Therefore, constipation cannot accurately predict risk in those patients who died. Case #64 had "colonic obstruction leading to dilatation and death" per GlaxoWellcome. Ogilvie's syndrome is characterized by massive dilation of the colon in the absence of a mechanical obstruction. This patient had Alzheimer's disease, no report of constipation or bloody diarrhea and was admitted due to change in her mental status. Her pathology report indicated ischemic colitis with necrosis. She underwent surgery within 10 hours of presentation to the ER and died within 4 days of surgery.

Case #21 was a 70 y.o. female with a history of IBS and diverticulosis who took Lotronex for 18 days, stopped it, was given Lomotil (ER report indicates that only one dose was taken), and presented to the ER 3 days after stopping Lotronex. A CT scan performed at admission to the hospital indicated a colonic perforation with abscess, diverticular disease and free air in the abdomen. She underwent a sigmoid colon resection that revealed a transmural perforation with ischemic colitis and she had stool in her pelvis. Her pathologic report indicated a recent thrombus in the mesenteric artery and vein, with no emboli or vasculitis. She had surgery within 12 hours after presentation and died less than 24 hrs following surgery. The sponsor argued that she had a hypotensive episode in the ER and that the colon ischemia was secondary and the colon perforation was due to diverticular disease.

Case #43 had an upper GI bleed possibly due to alendronate therapy. She did not have surgery, but repeat CT scan indicated gas in the portal vein and she was given supportive care.

One additional death case (Case #69) had indicated that the reporter was not sure if the patient was taking the drug around the time of illness. This patient had constipation and abdominal pain. She underwent colectomy for a ruptured colon and at surgery the entire colon was packed with solid stool.

Of the 10 surgery cases (including deaths, Table 5), 9 had presenting symptoms of abdominal pain, only 2 had presenting symptoms of constipation, and possibly 1 had bloody diarrhea. Therefore, once again, prospective complaints of constipation do not accurately predict risk in those patients who required surgery, and were found to be constipated at surgery.

Several illustrative surgical cases follow. Case #25 was treated with Lotronex, then stoppped, and was restarted following colonoscopy. Two weeks later she presented with abdominal pain and constipation. She underwent a colectomy and had evidence of ischemic colitis, bowel wall less than 0.1cm, and a colon full of stool. Case #61 had alternating type IBS, treated with 2 1/2 weeks of Lotronex. She presented with abdominal pain, no constipation, and underwent a colectomy for a perforated sigmoid colon and had fecal material in the abdomen. Case #65 had 1 month of Lotronex therapy and presented with abdominal pain and no constipation. She underwent a colectomy for a stercoral ulcer with perforation and ischemic necrosis and was noted at surgery to have copious amounts of hard stool in the colon. Case #74 had 6 weeks of Lotronex therapy; she presented with abdominal pain and no constipation. She had a colectomy and mural perforation of the colon with associated acute serositis was found on resection.

Of the 49 cases of ischemic colitis, only 9 (18%) had complaints of constipation at the time of event. Of the 21 cases of severe complications of constipation, 16 (76%) had complaints of constipation at the time of event. Constipation in the remaining cases was supported by radiologic, surgical, or pathologic evidence of constipation, i.e., colon full of hard stool. Obviously some patients that had severe complications of constipation were not able to recognize the signs or symptoms of constipation.

From a post-marketing risk management or a post-marketing safety assessment, it is irrelevant whether the ischemia is primary or secondary. The sponsor makes much of this distinction but we fail to see its importance.

6. GlaxoWellcome's argument that age is a risk factor

During the November 13, 2000 meeting, GlaxoWellcome acknowledged that the majority of the cases occurred in the "elderly" and that PRECAUTIONS for use in women over 65 would control the risk.

Two of the cases of ischemic colitis requiring surgery (Cases 25 & 74) were under 65 years of age and two of the cases of severe constipation requiring surgery (Cases 65 & 78) were under 65 years of age also (Table 2-2 & Table 5). Of the 49 cases of ischemic colitis, 36 (73%) were under 65 years of age. Of the 21 cases of severe complications of constipation, 12 (57%) were under 65 years of age.

The majority of cases as seen to date occurred in women less than 65 years of age. Therefore, a risk management program limiting use of Lotronex in women over 65 years of age will not prevent further occurrences of ischemic colitis or complications of constipation.

7. GlaxoWellcome's argument that controlling constipation will manage the risk

During the November 13, 2000 meeting with GlaxoWellcome, they did acknowledge that severe constipation results in significant morbidity and mortality. They claimed that controlling constipation will manage the risk of Lotronex therapy.

As summarized in Section 4 above, of the 3 cases that resulted in death, 2 had presenting symptoms of abdominal pain, only one had constipation, and none had bloody diarrhea (Table 5).

Of the 10 surgery cases (including deaths Table 5), 9 had presenting symptoms of abdominal pain (patient not reporting pain had Alzheimer's disease), only 2 had constipation complaints in the ER, and possibly 1 had bloody diarrhea. Of those cases that were classified as severe constipation, only 1 had constipation as a presenting symptom. In 3 cases the surgeon indicated that the colon was packed with stool at the time of surgery (i.e., constipated), and 1 case had radiologic evidence of impaction. These cases also clearly indicate that some of the patients with severe complications of constipation were unable to recognize constipation. Therefore, constipation would not have accurately predicted serious risk in those patients who died or required surgery.

Case #78, is a 39 year old female who was found at surgery to have extremely hard stool within the colon and sigmoid as well as formed stool in her abdominal cavity that had eroded into the abdomen. She underwent a second surgery 7 days later and pathology indicated ischemic necrosis of the bowel wall. In the case report, she did not have constipation nor did she verbalize complaints of constipation.

Case #65, is a 57 year old female who had a perforated sigmoid colon from a stercoral ulcer. Preoperative X-ray revealed copious amounts of stool throughout the colon. She underwent a colectomy and had large amounts of hard stool noted at surgery. On admission she was able to pass very small amounts of soft stool and no complaint of constipation was recorded.

Cases #78 & #65 above illustrate two cases that required surgery in which prospective constipation was absent as a presenting symptom. Once again, any risk management

program targeted to identify and manage constipation will be unsuccessful in managing the risk of serious adverse outcomes associated with Lotronex use.

8. Adverse and serious adverse events with other drugs, specifically those used to treat IBS

GlaxoWellcome argued at the November 13, 2000 meeting that there are serious adverse events associated with other drugs used to treat IBS. They cited the drug label Contraindications, Warnings, and Precautions sections of the labels for Bentyl (dicyclomine), Imodium (loperamide), Levsin (hyoscyamine), and Lomotil (diphenoxylate). In addition, they indicated that FDA AERS reports included complications of constipation, such as ileus, impaction, obstruction, and colitis for amitriptyline, diphenoxylate, and loperamide. They also included a table of "Deaths" from AERS 1969 - June 30, 2000 (a 31 year period) for Dicyclomine (30), hyoscyamine (32), loperamide (25), diphenoxylate (63), bismuth subsalicylate (19), and amitriptyline (382). The sponsor did not present any evaluation of the relevance of these reports, for example, the cause of death, concomitant medications, or disease being treated.

OPDRA evaluated the raw number of reports received in AERS from 1969 to present for 21 selected serious gastrointestinal events for several agents (loperamide, amitriptyline, diphenoxylate, hyoscyamine, and diclyclomine) used in IBS (Table 6).* There is extensive market experience with 3 of these 5 products: loperamide (approved 1976), amitriptyline (approved 1961) and dicyclomine (approved 1950). With loperamide there are 204 total reports of constipation, including 1 report of death, and 7 reports of hospitalization. With amitriptyline there are 78 total reports of constipation, including 4 reports of death, and 13 reports of hospitalization. With dicyclomine there are 10 total reports of constipation, including no reports of death, and 2 reports of hospitalization. In the 4 different intestinal perforation event categories, there are 8 total reports for loperamide, including 1 report of death, and 8 reports of hospitalization; there are 2 total reports for amitriptyline, including no reports of death, and 2 reports of hospitalization. In contrast there are no reports of intestinal perforation for dicyclomine or hyoscyamine. In the 3 different hemorrhagic colitis event categories, there was 1 report for loperamide, including 1 report of death and 1 report of hospitalization; there are 3 total reports for amitriptyline, including 2 reports of death and 2 reports of hospitalization. Again, there are no reports with this event for dicyclomine or hyoscyamine. With loperamide, there are 5 total reports of rectal bleeding, including no reports of death, and 1 report of hospitalization. With amitripyline, there are 2 total reports of rectal bleeding, including no reports of death, and 2 reports of hospitalization. With diphenoxylate, there is 1 total report of rectal bleeding, including no reports of death, and 1 report of hospitalization. Again, there are no reports of rectal bleeding for dicyclomine and hyoscyamine.

OPDRA evaluated the distribution of cases of ischemic colitis in AERS from November 1997 through October 2000 (Figure 3-1). Ischemic colitis as a search term in AERS did not exist before November 1997. A raw total of 180 cases of ischemic colitis was identified.* Forty-eight cases (27%) were associated with Lotronex, 7% with Imitrex, 4% with Premarin, and the remaining 62% with 78 different drugs. NO cases of ischemic colitis were identified for any other drugs used "off-label" to treat IBS, including Imodium, Lomotil, Valium, Librium, Levsin, and Levsinex. NO cases of ischemic colitis were identified with other 5-HT3 receptor antagonists, including Zofran (ondansetron),

* This data was generated using computer printouts, and some of the numbers may reflect duplicate reporting.

* This data was generated using computer printouts, and some of the numbers may reflect duplicate reporting.

Kytril (granisetron), and Anzemet (dolasetron). It should be recognized that these 5-HT3 receptor antagonists are currently approved for the prevention/treatment of emesis induced by cancer chemotherapy or preoperatively, and therefore are not used chronically like Lotronex, but only as single-dose or short-term treatment.

The argument that publicity has increased the number of reports can be refuted in that Rezulin has only one case of drug-associated ischemic colitis despite over 213 articles in major newspapers that discussed the drug and associated risk (Table 3-2). Two drugs already known to cause ischemic colitis, Imitrex and Premarin, have 12 and 8 reports respectively**.

9. Restricted Access Program for Lotronex

At the November 13, 2000 meeting, GlaxoWellcome mentioned a certification/education program similar to Accutane, although the details were not available. The Division of Gastrointestinal and Coagulation Drug Products presented a succinct summary of the limitations of such a program at the November 7, 2000 briefing to Dr. Woodcock. A restricted distribution plan will not manage the risk, but will only decrease the number of patients exposed and hence decrease the number of patients with a serious adverse outcome due to Lotronex. The risk is not managed, because the risk factors for serious adverse outcome have not been identified or categorized.

10. IBS is being minimized

One of GlaxoWellcome's consultants, Dr [redacted] of the [redacted] Division of Digestive Diseases, indicated that some people may look at IBS as "not a real disease" or a "trivial disease". IBS is truly a disease that has significant morbidity and compromises the quality of life of some patients. The natural history of IBS however is not comprised of bleeding that requires transfusion (Case #15 & #73) or surgery for constipation, either with (Cases #9, #21, #25, #64, #74) or without (Cases #58, #61, #65, #69, #78) resultant bowel ischemia. IBS is not associated with ischemic colitis if untreated. IBS does not lead to surgery, does not shorten the life span and does not cause death. Differentiating the symptoms of IBS from the symptoms due to the serious adverse consequences of Lotronex therapy is impossible. Early warning of the dire side effects of this drug is clearly not feasible.

11. CONCLUSIONS

The warning signs and symptoms of ischemic colitis or colonic ischemia are not always clear, not always typcial, and do not always occur. The reversibility or moderation of ischemic colitis or colonic ischemia has not been established. The signs and symptoms of an adverse effect are too similar to those of the disease being treated and/or the desired pharmacologic effect (i.e., "constipation" to relieve diarrhea). Constipation is **not** necessarily the major risk factor for ischemic colitis or colonic ischemia or colon resection. Any risk management program entirely centered on predicting and preventing constipation will not manage the risk from Lotronex therapy. The basic premise of the entire risk management program is as follows: if you can predict constipation, you can manage constipation, and if NOT, you undermine the whole risk management program.

** This information is from IMS HEALTH National Prescription Audit Plus (NPA) ™ and National Disease and Therapeutic Index (NDTI) ™ and is not to be used outside of the FDA without prior clearance from IMS HEALTH.

The only acceptable risk management program would have to show promptly and persuasively a cessation of deaths, colectomies, severe and serious complications of treatment that were unknown in the long history of IBS in patients taking other therapy, whether or not those therapies were effective.

From our analysis there are no known risk factors to predict either ischemic colitis or severe constipation, so any risk management strategy that focuses on the patient's age or the management of constipation will fail to manage the risk in the majority of patients exposed to Lotronex.

Kathleen Uhl, M.D.
Acting Division Director

Zili Li, M.D., M.P.H.
Medical Epidemiologist

Ann Corken Mackey, R.Ph., M.P.H.
Safety Evaluator

Paul Stolley, M.D., M.P.H.
Epidemiology Consultant

ATTACHMENT 1

WHAT IS KNOWN ABOUT THE RISK OF ALOSETRON

Ann Corken Mackey, Zili Li and Paul Stolley
OPDRA Alosetron Risk Assessment Group

November 13, 2000

1. **Four Key Questions:**
   (a) What is known about the risk of alosetron now?
   (b) What has changed regarding patterns of alosetron-associated ischemic colitis or severe constipation since the GI Advisory Committee meeting on June 27, 2000?
   (c) What is the evidence that those adverse events and associated serious outcome, such as bowel surgery and death are drug related?
   (d) Is a risk management strategy feasible?

2. **Methodology:**
   (a) Data Source:
   (1) Data provided by Adverse Event Reporting System (AERS) at FDA
   (2) Drug utilization data provided by IMS Health
   (b) Case Definition:
   (4) **Ischemic Colitis:** A diagnosis of ischemic colitis, ischemic changes or necrosis of colon based on any or a combination of the following: (1) clinical judgement, (2) endoscopic examination or (3) pathology report;
   (5) **Severe Constipation:** constipation or suspected constipation that led to ER visit, hospitalization, or complications, including but not limited to, fecal impaction, bowel obstruction, necrosis or rupture.
   (c) Inclusion Criteria:
   All ischemic colitis and/or severe constipation cases reported to FDA through MedWatch or by Glaxo Wellcome before November 10, 2000.
   (d) Exclusion criteria:
   The key event cannot be independently verified by FDA.

3. **Findings:**
   (a) Risk of alosetron: two dimensions - incidence and severity. This assessment focuses on severity. Refer to question A (page 2).
   (b) Changes since AC meeting on June 27, 2000: Increased severity. Refer to Question B (page 3).
   (c) Evidence supporting a causal relationship: Epidemiological and Individual Assessment; Refer to question C (page 4-6).
   (d) Current risk management strategies: Refer to Question D (page 7).

4. **Conclusions:**
   (a) The pattern of reported cases of ischemic colitis cannot be reasonably explained by anything but a true effect between the drug and the event;
   (b) Death is no longer a speculation or a remote possibility, but a reality. The cases of ischemic colitis that led to necrotic or ruptured bowel requiring surgery are also a reality;
   (c) No pattern has emerged with regard to factor or factors that can provide a meaningful prediction for those patients who developed ischemic colitis or constipation that required surgery.

Question A: What is known about the risk of alosetron now?

Table 1-1. Number of alosetron-associated cases of ischemic colitis and severe constipation, United States, cumulative, week ending November 10, 2000 (36th week of the marketing)

Key Adverse Events	Ischemic colitis	Severe constipation	Total
Number of reported cases	49	21	70
Cumulative number of prescriptions*	435,000		
Report rate per million prescriptions	113	48	161

* Estimated number of prescriptions dispensed between March and October 2000. Data was provided by Glaxo Wellcome at a Safety Presentation to FDA's GI division on October 25, 2000

Table 1-2. Severity of alosetron-associated cases of ischemic colitis and severe constipation, United States, cumulative, week ending November 10, 2000 (36th week of marketing)

Selected Outcomes[1]	Key Adverse Events[1]			
	Ischemic Colitis (n=49)		Severe Constipation (n=21)	
	Number	Percentage	Number	Percentage
ER visit without hospitalization	2	4%	2	10%
Hospitalization	30	65%	14	67%
Blood transfusion without surgery	1	2%	1	5%
Bowel obstruction without surgery	0	0	6	29%
Disimpaction performed	0	0	3	14%
Surgery due to obstructed, necrotic, or ruptured bowel	5	11%	5	24%
Death[2]	2	4%	1	5%

1. Selected outcomes are not mutually exclusive; the key adverse events are mutually exclusive.
2. There were two additional death cases that did not meet the criteria; therefore, the total number of death cases as of November 10, 2000 is five.

Table 1-3. Diagnostic certainty of alosetron-associated cases of ischemic colitis, United States, cumulative, week ending October 28, 2000 (34th week of marketing)

Diagnostic Certainty of Ischemic Colitis	Number	Column Distribution	Cumulative Distribution
Both histological and endoscopical evidence of ischemic colitis or ischemic change or necrosis	14	29%	29%
Endoscopical evidence of ischemic colitis or ischemic change or necrosis	8	16%	45%
Histological evidence of ischemic colitis or ischemic change or necrosis	13	27%	72%
Radiological evidence of ischemic colitis or ischemic change or necrosis	3	6%	78%
Ischemic colitis without above evidence*	11	22%	100%
Total number of cases	49	100%	

* Among those 11 cases, one was a surgical case that will be discussed later. Five cases had both abdominal pain and bloody diarrhea. Only one of those cases was a direct report from consumer.

Question B: What has changed since the GI Advisory Committee meeting on June 27, 2000?

Table 2-1. Changes in severity of alosetron-associated provisional cases of ischemic colitis and severe constipation, United States, before and after Advisory Committee Meeting on June 27, 2000 (includes post-marketing, non-study cases only).

Selected Outcomes	Ischemic Colitis		Severe Constipation	
	Pre-AC Meeting (n=5)	Post-AC Meeting (n=44)	Pre-AC Meeting (n=4)*	Post-AC Meeting (n=17)
Blood transfusion without surgery	0	1	0	1
Surgery due to obstructed, necrotic, or ruptured bowel	0	5	2	3
Death	0	2	0	1

* The original number was five cases; one of the constipation cases did not meet the case definition.

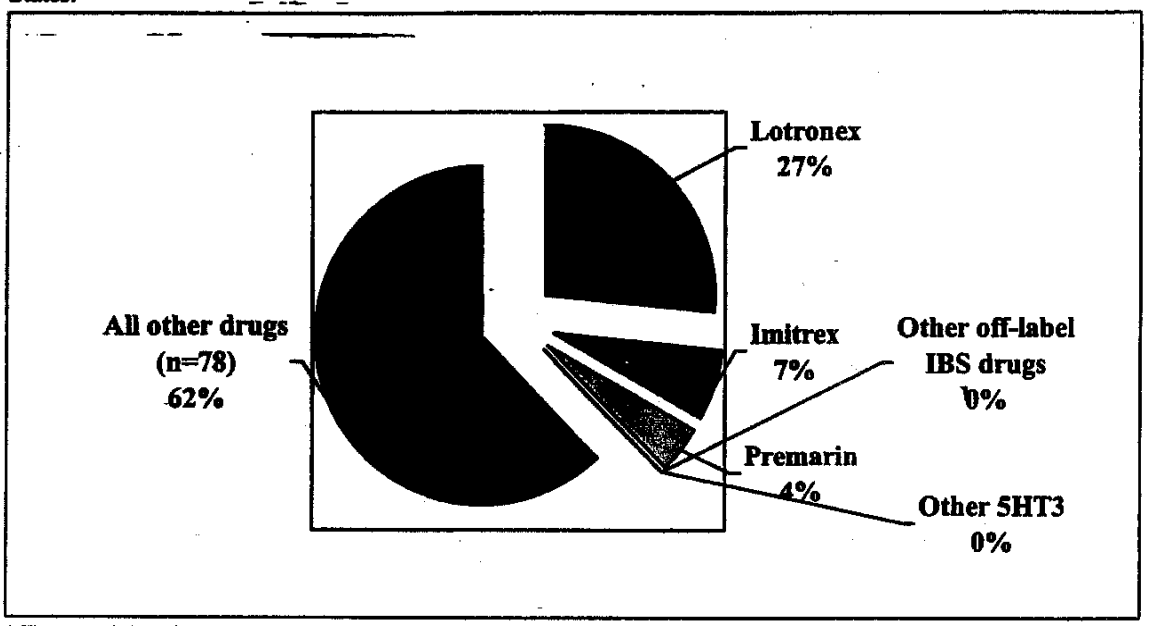
Table 2-2. Changes in severity of alosetron-associated surgical cases of ischemic colitis and severe constipation, United States, before and after Advisory Committee Meeting on June 27, 2000 (includes post-marketing, non-study cases only).

Items	Number of Reported Cases	
	Before Advisory Committee Meeting (n=2)	After Advisory Committee Meeting (n=8)
Age: % < 65 years old	0/2	4/8
Colectomy	1/2	8/8
Sigmoid colon only	2/2	5/8
Death	0/2	3/8

Question C: What is the evidence that those adverse events and associated serious outcome, such as bowel surgery and death, are drug related?

1. Epidemiological Assessment:

Figure 3-1. Distribution of reported cases of ischemic colitis* by the suspected drug, according to FDA's Adverse Event Reporting System (AERS) data** between November 1997 and October 2000, United States.



* The count is based on a search in AERS for the cases that contained the term "Ischemic colitis" in either initial or follow-up reports submitted to FDA. Therefore, the number of cases could be different from the number obtained after manual case review. Ischemic colitis as a search term in AERS did not exist before November 1997.

** Note that no reports of ischemic colitis were found in AERS between November 1997 and October 2000 for other drugs used "off-label" to treat IBS (e.g. Imodium, Lomotil, Valium, Librium, Levsin, and Levsinex) or other 5-HT_3 drugs, including Zofran, Kytril, and Anzemet.

Table 3-1. Reported cases of drug-associated ischemic colitis per million prescriptions for selected drugs, AERS and IMS data, United States, November 1997 and October 2000

	Lotronex	Imitrex	Premarin
Date of Approval	2/9/00	12/28/92 6/1/95	Prior 82
Reported Cases	49	12	8
Surgical cases	5	1	0
Estimated number of prescriptions (X 1,000)*			
Reported rate of ischemic colitis per million prescriptions			

* Estimated number of prescriptions dispensed between November 1997 and October 2000. Data cannot be released from FDA without prior approval from IMS Health.

Table 3-2. Reported cases of drug-associated ischemic colitis per million prescriptions for selected drugs, AERS and IMS data, United States, November 1997 and October 2000.

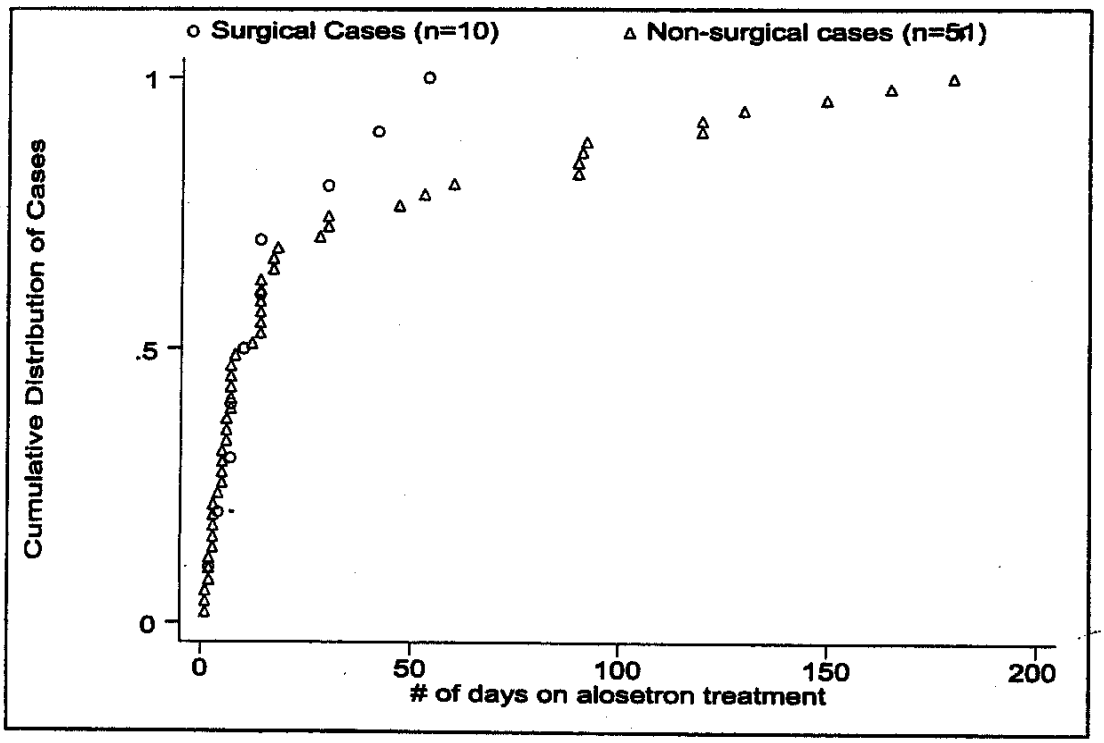
	Lotronex	Vioxx	Rezulin	Lotronex*
Date of Approval	2/9/00	5/20/99	1/29/97	2/9/00
Media Effect†	17 articles	--	213 articles	1 article
Reported Cases	49	5	1	23
Surgical cases	5			1
Estimated number of prescriptions (X 1,000)$				
Reported rate of ischemic colitis per million prescriptions				

* Lotronex-associated ischemic cases reported before August 31, 2000.

† Articles that appeared in major newspapers that discussed the drug and associated risk.

$ Estimated number of prescriptions dispensed between November 1997 and October 2000. Data cannot released from FDA without prior approval from IMS Health.

Figure 3-2. Cumulative distribution of alosetron-associated surgical and non-surgical cases by reaction onset (days), United States, week ending October 28, 2000.



2. Individual Assessment:

(a). FDA CASE #9 (Manufacturer control number A0121632A)

A 69-year-old female, one week after the treatment with Lotronex, developed an epidsode of ischemic colitis at transverse colon that was supported by both colonscopy and pathology report. The drug was reported to be discontinued. Approximately 6 weeks later, she was hospitalized with abdominal pain. Patient underwent a right hemicolectomy associated with large bowel obstruction secondary to ischemic stricture at mid transverse colon. Pathology report confirmed a broad area of acute ulceration that is compatible with ischemic colitis of right colon. Occasional small vessels with a thrombus are seen at the base of the ulcer. Patient had a normal colonscopy examination on December 15th,1999. On March 17, she was diagnosed by her GI specialist as having IBS and started Lotronex 1 mg b.i.d. One month after the first episode of ischemic colitis, her GI specialist raised a possibility of ulcerative colitis or Crohn's colitis due to unclers on her right hip and abdomen. One week later, GI specialist also raised a possibility a vasculitis with immune complex disease. Only diagnostic test received at FDA was a pathology report on 5/9/00 that showed epidermal ulceration with eschar formation on a specimen from right midtrunk. There is no evidence to suggest vasculitis.

Chain of Events: Drug-induced ischemic colitis - stricture at prior ischemic site - bowel obstruction - colectomy

(b). Ischemic colitis case: (FDA case #21, manufacturer number A0126868A)

A 70-year-old female, a week after beginning treatment with Lotronex, presented to ER with a sudden onset of abdominal pain, nausea and vomiting, but no bloody diarrhea. An X-ray showed normal bowel gas pattern and stool within the large bowel. CT showed evidence of large pelvic and lower abdominal abscess most likely related to diverticulitis. The patient became hypoxic, hypotensive, and acidotic; she was intubated in the ER and brought for an emergency surgery where a perforated sigmoid colon was found with solid stool in the pelvis. A sigmoid colon resection with colostomy was performed and the pathology report showed ischemic colitis and transmural perforation with associated diverticulosis. Diverticulitis was not mentioned in the pathology report. Mesenteric vein and arteries showed recent thrombus; but were negative for emboli and tumor. The patient became septic and died on the second hospital day. She was in good health over all and had no history of diabetes and heart disease. She was taking estrogen but had been on it as long as her primary care physician could remember. The manufacturer's follow-up report stated that the physician suspected that the events could have been due to impaction and were possibly related to the use of alosetron.

Chain of Events: Drug-induced ischemic colitis - secondary infection - rupture - colectomy

Question D: Is a risk management strategy feasible?

Table 4-1. Indications, contraindications and presenting symptoms for patients who required surgery and/or died.

Items	Ischemic colitis	Severe Constipation
Indications		
Female	5/5	5/5
Diarrhea-predominant IBS	4/5	4/5
Contraindications		
Current constipation	0/5	0/5
History of chronic, severe constipation; obstruction; toxic megacolon; GI perforation; adhesions; ischemic colitis or active diverticulitis	0/5	0/5
Presenting symptoms at ER		
Abdominal pain	4/5	5/5
Bloody diarrhea	0/5	1/5
Constipation	1/5	1/5

2. Illustrative cases of constipation:

Case #78: A 39-year-old female presented to the ER because of sudden onset of severe abdominal pain. While in the ER, she became hypotensive and was intubated. It was reported that the ***patient did not have constipation nor did she verbalize complaints of constipation.*** However, during exploratory laparotomy she was found to have an extremely hard stool within the colon. It appeared that the stool had eroded into the abdomen, as formed stool was discovered. The area at the perforation was noted to have complete ischemic necrosis. A sigmoid colectomy was performed.

Case #65: A 57-year-old female, 4 weeks after beginning treatment with Lotronex, presented to the ER due to crampy abdominal pain that had started five days earlier. ***She was able to pass very small amounts of soft stool at admission and no complaint of constipation was recorded.*** However, X-ray revealed copious amounts of stool throughout the colon. One-day later, she was taken to surgery and perforated stercoral ulcer of the sigmoid colon was found. The patient's colon was found to have copious amounts of hard stool.

Table 5. Characteristics of the Ten Surgical Cases

Characteristics of Surgical Cases	Case #9	Case #21	Case #25	Case #64	Case#74	Case #58	Case #61	Case #65	Case #69[3]	Case #78
FDA Classification	Ischemic colitis	Ischemic colitis	Ischemic colitis	Ischemic Colitis	Ischemic Colitis	Constipation	Constipation	Constipation	Constipation	Constipation
Presenting symptom (ER)										
Abdominal pain	Yes	Yes	Yes	No[1]	Yes	Yes	Yes	Yes	Yes	Yes
Bloody diarrhea	--	--	--	--	--	--	--	--	--	Yes[6]
Constipation	--	--	Yes	--	--	Yes	--[5]	--	--	--
Clinical impression (before surgery)	Ischemic colitis	Diverticulitis	Not Available	Acute abdomen, bowel obstruction	Probable ischemic colitis or a colitis with perforation	Sigmoid diverticulitis	Not available	Colonic atony secondary to Lotronex	Acute abdomen, r/o diverticulitis; r/o ischemic bowel	Not available
Radiologic examination	Not available	CT revealed a perforated colon	x-ray showed no free air, no dilation; colon full of stool	x-ray showed distended loops of small bowel	CT: thickened colon at descending colon	x-ray showed that colon was full of stool	CT showed air fluid levels and a mass outside the bowel	Copious amounts of stool in colon; no diverticulitis	CT showed some bowel wall thickening	Not available
Endoscopic examination	Ischemic colitis	Not done	Not done	Not done	Not done	Not done	Not done	Not done	Not done	Not done
Report of Operation	(on 6/5/00, 6 weeks after this episode); bowel obstruction due to ischemic stricture at transverse colon	Perforated colon at the rectosigmoid partially contained within the mesentery, however, evidence of frank feculent peritonitis	Not available	Ogilvie's syndrome[2] with necrotic sigmoid	Sigmoid colitis with air in the mesentery and mesenteric infection	Not available	Perforated sigmoid colon and fecal material in the peritoneum	No sign of ischemic change of diviticulitis; Stercoral ulcer of colon	Ruptured colon; entire colon packed with solid stool, feeling like a rock	Extremely hard stool within colon and sigmoid; it appeared that stool had eroded into the abdomen
Pathology report	Not available for this episode; however surgical specimen on 6/5/00 showed right colon - consistent with ischemic colitis	Ischemic colitis including transmural perforation; associated diverticulos-is; Mesenteric veins and arteries showed recent thrombus	Change consistent with ischemic colitis; Bowel wall thinned in many areas to the point of near translucency	Mucosal erosion with gland atrophy and acute inflammation suggestive of an ischemic colitis	Mural perforation of colon with associated acute serositis; acute fat necrosis and pericolic microabscess formation	Not done at time of surgery	Not available	Ulcer with perforation and necrosis (sigmoid colon); acute ulcer and necrosis with ischemic changes (left colon)	Diverticu-losis and diverticulitis with perforation	Two segments of colon showing focal area of perforation and peritonitis associated with epithelial invagination

Table 5. (Continued)

Characteristics of Surgical Cases	Case #9	Case #21	Case #25	Case #64	Case#74	Case #58	Case #61	Case #65	Case #69[3]	Case #78
Demographics										
Age	69	70	54	67	48	68	72	57	82	39
Gender	F	F	F	F	F	F	F	F	F	F
Indication[7]	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes
Date of Event	3/22/00	7/31/00	8/15/00	9/9/00	8/18/00	4/7/00	4/6/00	8/29/00	8/24/00	6/17/00
Date of Initial Report	6/12/00	9/6/00	9/11/00	10/8/00	9/7/00	5/3/00	5/23/00	10/3/00	10/10/00	7/7/00
Drug Exposure Data										
Days on Rx before the key GI event	7	7	14	54	42	2	4	30	10	14
Dose	2 mg/day	2 mg/day	Unknown	1 mg/day	2 mg/day	2 mg/day	2 mg/day	2 mg/day	2 mg/day	2 mg/day
Surgical Information										
Location of necrotic or ruptured colon	Right and transverse	Sigmoid	Right	Sigmoid	Sigmoid	Sigmoid	Sigmoid	Sigmoid and left	Sigmoid	Sigmoid
Type of surgery	Colectomy	Colectomy	Colectomy	Colectomy	Colectomy	Colostomy	Colectomy	Colectomy	Colectomy	Colectomy
Mesenteric artery/vein Thrombus	Yes	Yes	--	No	No	--	--	No	No	No
Potential Confounding										
Estrogen	Yes	Yes	--	Yes	--	--	--	--	--	--
Diverticulitis	No	No	No	No	No	No	--	No	Yes	No
Diverticulosis	No	Yes	No	No	No	Yes	--	No	Yes	No
Others	Vasculitis ?	No	Raynaud's syndrome ?	Ogilvie's syndrome[2]	No	Polyps	No	No	No	No
Physician assessment re. association of event with alosetron	--	Possible	--	--	Possible[4]	--	Possible	Possible[4]	Not related	Possible
Prior colonscopy before treatment	Negative	Diverticu-losis, polyps	--	--	Negative	--	--	--	Diveticulosis	--
Death	No	Yes	No	Yes	No	No	No	No	Yes	Yes

1. Patient had Alzheimer's disease and was not be able to provide this information.
2. Ogilvie's syndrome (acute pseudo-obstruction of the colon) is a massive colonic distention in the absence of a mechanically obstructing lesion.
3. Case #69 is a legal case.
4. As stated in the medical records.
5. Patient did complain of constipation in the Dr.'s office.
6. Small amount of fresh blood in stool.
7. Labeling followed when alosetron was prescribed (e.g., females with diarrhea-predominant IBS).

Table 6. SELECTED GASTROINTESTINAL EVENTS FOR SELECTED AGENTS USED IN IRRITABLE BOWEL SYNDROME (IBS) FROM THE ADVERSE EVENT REPORTING SYSTEM (AERS)[1]

	Total # / # Deaths / # Hospitalized				
EVENT (MEDRRA PREFERRED TERM)	LOPERAMIDE IMODIUM® AND OTHERS Approved 1976	AMITRIPYLINE ELAVIL® AND OTHERS Approved 1961	DIPHENOXYLATE / ATROPINE LOMOTIL®[2] AND OTHERS	HYOSCYAMINE LEVSIN®[3] AND OTHERS	DICYCLOMINE BENTYL® AND OTHERS Approved 1950
SOC GASTROINTESTINAL DISORDERS: TOTAL	1635/49/159	771/58/173	82/9/22	77/1/22	137/1/10
COLITIS HAEMORRHAGIC	1/1/0	2/2/1	1/1/0	0	0
COLITIS NOS	14/0/12	5/1/3	3/0/1	0	1/0/0
COLONIC HAEMORRHAGE	1/0/1	0	0	0	0
COLITIS ISCHAEMIC[4]	0	1/0/1	1/1/1[5]	0	0
COLONIC PERFORATION	2/0/2	0	1/1/1	0	0
CONSTIPATION	204/1/7	78/4/13	5/0/0	2/0/0	10/0/2
FECAL IMPACTION	5/0/3	3/0/3	1/1/1	1/0/1	0
GASTROINTESTINAL NECROSIS	2/0/1	2/0/2	0	0	0
GASTROINTESTINAL OBSTRUCTION	1/0/1	3/1/3	0	0	0
ILEUS	53/11/25	15/2/9	10/0/3	2/0/2	3/0/2
ILEUS PARALYTIC	4/2/1	3/1/2	0	0	0
INTESTINAL OBSTRUCTION NOS	27/1/21	10/2/8	3/0/2	1/0/1	0
GASTROINTESTINAL PERFORATION	0	0	1/0/1	0	0
INTESTINAL PERFORATION NOS	6/1/6	1/0/1	2/1/0	0	0

[1] Some of the numbers presented may reflect duplicate reports. One report may contain more than one event, so these numbers are not mutually exclusive. AERS contains data from 1969 to present. Data are reflective of information in AERS from approval date of drug (or from 1969 for drugs approved before that date) to 11/14/2000.
[2] Drug approved prior to 1969
[3] Hyoscyamine is a prescription drug available pre-1938 (no NDA; "Grandfather Drug")
[4] MedDRA Preferred Term (PT) Colitis Ischaemic available as term for coding adverse events November 1997
[5] This patient was a 70 yo female who also received Lotronex®.

	Total # / # Deaths / # Hospitalized				
EVENT (MEDRRA PREFERRED TERM)	LOPERAMIDE IMODIUM® AND OTHERS Approved 1976	AMITRIPYLINE ELAVIL® AND OTHERS Approved 1961	DIPHENOXYLATE / ATROPINE LOMOTIL®[2] AND OTHERS	HYOSCYAMINE LEVSIN®[3] AND OTHERS	DICYCLOMINE BENTYL® AND OTHERS Approved 1950
INTESTINAL ULCER PERFORATION	1/0/1	0	0	0	0
LARGE INTESTINAL PERFORATION NOS	1/0/1	1/0/1	0	0	0
RECTAL BLEEDING	5/0/1	2/0/2	1/0/1	0	0
SMALL INTESTINAL OBSTRUCTION NOS	1/0/1	0	0	0	0
SMALL INTESTINAL PERFORATION NOS	0	0	0	0	0
TOXIC DILATATION OF COLON	1/0/1	0	0	0	0