this when the pharmacist gives them their counseling? That is where it should be, it should be at the pharmacy counseling. The physician may decide on what to give but the pharmacist is going to give it month to month, in an out.

Usually in counseling -- I know in New York State, where I am, in a very litigious area, everyone signs for everything, and they sign that they want counseling or not. Shouldn't the patient have basically an informed consent so that they, as the ones who determine whether they have the illness or not, be informed even more than the professionals?

There is one other comment that I would like to make, and that is the use of the databases that you are talking about. You talk about Medicaid, and my experience is with the New York State Medicaid -- these are claims databases. These are not scientific databases. They are really good for claims on drugs, but for doing scientific research they have a lot of shortcomings. Thank you.

DR. KENT: I will answer the first part and ask Dr. Andrews to talk about the databases. Lotronex will have a patient package insert that we are discussing with the FDA. It is not in your briefing document today because it is early in its formation but there will be a patient package insert.

In terms of signing an informed consent, we don't think that is appropriate. If you want to do that for Lotronex, then most of the drugs you prescribe you would have to have an informed consent for, if you think about their potential complications.

We do agree that counseling of the patient is very important. From our perspective, the two professionals who should be doing that are, number one, the physician -- and we keep talking about how the physicians aren't doing their job but that is what they are licensed to do; that is what they are supposed to do. If they don't do that, then medical licensing boards and, unfortunately, malpractice lawyers and things like that -- we do have checks and balances but we have an intermediary who is supposed to be teaching patients. We can do a certain amount that you have seen us present, and we certainly welcome all of your suggestions about the program that we are proposing. We cannot sit there, in the physician's office, with the patient and say, "you, sir, are a thoughtful, careful, understanding physician and you have portrayed this correctly to your patient," and "you, sir," or "ma'am, are a sloppy, uncaring physician and this patient is in great danger." We can't be there to do that.

Let me ask Dr. Andrews to talk about the databases.

DR. ANDREWS: Well, you are absolutely right, not all databases are robust for all research questions. What I can say is that we have selected for our studies databases that have a proven track record, as well as investigators who have a very careful approach to using these databases, and each of these has been very useful in the past in evaluating specific issues relating to drug safety.

The key issue is to take the research questions and make sure that you develop the appropriate methodology, including the appropriate database, and if the outcomes can be well defined, then utilize those databases that are appropriate. In the case of ischemic colitis, the difficulty is that there is a broad spectrum of disease including acute and transient cases that may not even come to medical attention. We will miss those cases -- absolutely, but we have confidence that we will be able to evaluate cases representing symptomatology that could be possible cases, as well as those cases that are defined. In terms of complications of constipation, serious complications such as perforation, should be very easy to identify in a database, supplemented with, again, the ability to abstract medical records for further detail.

DR. HANAUER: You have a follow up?

DR. BLUM: Just one follow up, in using those databases, have you decided on any way to look for

hepatotoxicity? Whereas the constipation and the ischemic colitis are very vocal, the hepatotoxicity can be very silent.

DR. ANDREWS: A very good question. We have not explored that in great detail because we don't feel we have a signal in that area. There is certainly a lot of research relating to use of a variety of methods in epidemiology to evaluate hepatotoxicity.

DR. HANAUER: Mr. Hull?

MR. HULL: I just wanted to make one follow-up comment to Dr. Kent's reference to the patient package insert. The patient package insert is a comprehensive part of our communications program, and will be made available not only in the patient sample distributed by physicians, but also in the form of a separated patient package insert available at the pharmacy level. So, we have multiple mechanisms and use of repetitive mechanisms to ensure patients get the appropriate information.

DR. HANAUER: Dr. Kramer?

DR. KRAMER: This is a related question. In terms of your communications package, some of the points of communications or channels are directed to the patient and one thing I noticed was that yellow important information sticker. That seems a little non-specific to me, and I wonder if there is any research, if there is knowledge on

the effect that that sticker has as opposed to other messages, including size of the sticker and what it says. The patient would have no way of knowing what that information inside is. It might be a more detailed description of all the benefits to the drug. For example, how would a patient know that there is a reference to actual warnings inside?

MR. HULL: Thank you for the question. I would like to reenforce that the entire communications program is a multi-faceted program and it doesn't rest upon any one component; it is the integration of all the components. I tried to elucidate that the components of the program that we have for the healthcare practitioners as well as the office staff, the hospital and retail pharmacies, as well as the patients all work together. Then we use those vehicles in a repetitive manner to communicate the important information around appropriate patient selection and management of constipation, as well as the early identification of ischemic colitis. So, we see these as a comprehensive effort to get important information not only to healthcare professionals but to patients as well.

DR. HANAUER: Last question and then we are going to take a break.

MR. LEVIN: In terms of the patient package insert, are we talking about a medication guide as defined

in regulation as to format?

DR. KENT: We haven't discussed that with the FDA. What we are working on is a patient package insert. Again, our understanding is the med. guide, at least as defined by FDA, would be used in a very select number of drugs, drugs with very serious risk-benefit problems. Based on that definition, again, we would maintain this drug does not fall into that category.

DR. HANAUER: That is one of the final questions that is coming to us for recommendations to the agency. We will take a 15-minute break and resume at 11:10.

[Brief recess]

DR. HANAUER: We will have the FDA presentation that is going to be initiated by Dr. Victor Raczkowski.

FDA Presentation

Benefit-Risk Reevaluation of Marketed Drugs

DR. RACZKOWSKI: Dr. Hanauer, members and guests of the advisory committee, ladies and gentlemen, FDA is convening this meeting of the Gastrointestinal Drugs Advisory Committee to discuss benefit-risk reevaluation of marketed drugs.

[Slide]

As you know, FDA approved Lotronex, for treatment of irritable bowel syndrome in women in whom diarrhea was a predominant bowel symptom, in February of this year. Since

then, FDA has received additional safety reports suggesting that a reevaluation of the benefit-risk profile of Lotronex is indicated.

[Slide]

FDA's presentations will have several themes. First, we will discuss the benefit-risk evaluation of Lotronex. We will specifically talk about the potential benefits of Lotronex, the potential risks of Lotronex and, importantly, how the benefit and risk are combined for Lotronex.

We will also discuss risk management options that are available, such as labeling changes including medication guides, patient education, advertising, drug distribution limitations and withdrawal.

Finally, we will discuss assessing the impact of risk management interventions. In other words, FDA believes that it is not sufficient to just institute a risk management intervention without evaluating whether or not that intervention is having the desired impact or desired goal. Thus, in order for risk management interventions to be meaningful, they should have established goals and should be followed by an evaluation of whether those goals have been achieved.

[Slide]

There will be several FDA presentations. I will

begin by talking primarily about the benefit reevaluation of Lotronex. I will be followed by Dr. Hugo Gallo-Torres who will discuss the safety aspects related to gastrointestinal serious adverse events associated with Lotronex.

[Slide]

I will then return and discuss various risk management options. Subsequently, Dr. Nancy Ostrove will specifically discuss medication guides.

[Slide]

Dr. Evelyn Rodriguez will discuss risk intervention studies, including two case studies in which labeling has been used and the desired impact of labeling has been assessed. Finally, I will summarize the issues.

[Slide]

As stated in the package insert, Lotronex is indicated for the treatment of irritable bowel syndrome in women whose predominant bowel symptom is diarrhea. The indication for Lotronex in the currently approved labeling states that the safety and effective of Lotronex in men have not been established.

[Slide]

The primary issues associated with benefits of Lotronex revolve around two principal questions: Limiting the administration of Lotronex to target populations and/or limiting the administration of Lotronex only to responders.

[Slide]

Regarding the first issue, if a drug is not effective in a population taking the drug, then those patients experience risk from taking the drug without benefit. Similarly, going to the second issue, if a drug is not effective in an individual taking the drug, that is, if a patient is a non-responder, that patient experiences risk without benefit.

[Slide]

Let us look at the first issue, limiting Lotronex administration to the desired target population.

[Slide]

What is the target population for Lotronex? As stated in the indication, Lotronex is indicated for women with diarrhea-predominant IBS. It is not indicated for women with other subtypes of IBS. As an example of this, and there were some questions that came up in the previous discussion, some subgroup analyses from the two principal phase III studies performed by the sponsor suggested that Lotronex may not be effective in women with IBS who have a pattern of alternating diarrhea and constipation. In other words, when the primary endpoint was assessed between the placebo group and the Lotronex treatment group in the subgroup of patients, the results were similar in terms of the percent of patients responding to either placebo or to

Lotronex.

[Slide]

There is also a need for a legitimate diagnosis of irritable bowel syndrome. Lotronex should be used only in women with a genuine diagnosis of diarrhea-predominant irritable bowel syndrome. It should not be used in women in whom a casual diagnosis of IBS has been made. It should also not be used in patients who have been misdiagnosed with IBS because of symptoms that are masquerading as IBS.

And, we are interested in hearing the advisory committee's input as to what sorts of things we can do from a risk management perspective that can ensure that patients who are administered Lotronex are those patients who do have a genuine, legitimate diagnosis of diarrhea-predominant irritable bowel syndrome. Again, patients who are receiving Lotronex because of an inappropriate, casual diagnosis or a misdiagnosis of IBS will be exposed to the risks of the drug but to its potential benefits. So, we are also interested in finding from the advisory committee whether there are any specific criteria or tests needed for selection of women who might benefit from the drug's use.

[Slide]

Lotronex is not indicated for men. Data from phase II trials suggested that Lotronex is not effective in men even at dosages eight times that used in women.

Lotronex is not indicated for pediatric use, and this is primarily just from a lack of data in that population.

[Slide]

Moving to the second issue, limiting the administration of Lotronex to responders --

[Slide]

Lotronex is a drug with a modest beneficial effect in terms of the percentage of patients who benefit from the drug. I will explain the issue and then I will run through the data demonstrating this. Forty percent of women with diarrhea-predominant IBS who took Lotronex did not improve. Another 40 or 50 percent of those patients improved spontaneously or due to other factors, for example, a so-called placebo effect. Improvement attributable to Lotronex was only demonstrated in about 10-20 percent of patients.

[Slide]

The data on this slide and the following slide come from pages 180 and 181 of the briefing document. These data are in tabular form. This is the FDA's briefing document. Similar data in graphical format can be found on page 259 of the briefing document from the approved package insert, which is page 6 of the package insert, and Glaxo Wellcome has presented that data graphically, or very similar data earlier today.

Let me run through these data. There were two

principal phase III efficacy studies demonstrating the efficacy of Lotronex. These data, shown on this slide are only the data from the diarrhea-predominant subgroup, looking at the primary endpoint of a clinical trial, the percentage of patients who experienced adequate relief of abdominal pain or discomfort, and it is expressed in terms of monthly relief. These particular analyses were done by the FDA statistician, and here is a last observation carried forward analysis, and they are largely consistent with the data that have been presented at previous advisory committees by the company and they are currently in the package insert.

Both trials were 3-month trials in terms of when the patients were randomized to treatment, either placebo or to Lotronex at 1 mg b.i.d. Again, all the patients in the trial were women with diarrhea-predominant IBS. If we look at the response to placebo, we see that roughly 40 percent of women at any given month had an apparent response based on the primary endpoint. If we look at the Lotronex response, we see a slight increment at month 1, from 39 percent to 50 percent. Thus the effect that is attributable to Lotronex is only the difference between the two, about 11 percent. Similarly, at month 2 the difference between 58 percent on Lotronex and 43 percent shows an effect attributable to Lotronex of only 15 percent. Finally, at

month 3, 60 percent minus 41 percent, and an effect attributable to Lotronex of only 19 percent.

If you ask the question then of all the women who responded or who appeared to respond what percentage of them had a response that was attributable to placebo or to other spontaneous factors, those results are shown in column 3, simply by dividing 39 by 50 percent. You can see that between 68 percent and 78 percent of patients in this trial had an effect that was not attributable to Lotronex but was attributable to other factors, such as spontaneous improvement or other unknown factors related to the trial. In other words, out of 10 women who appeared to benefit from the effects of Lotronex, 7 or 8 of them are not improving from the effects of Lotronex but, rather, they are improving spontaneously or due to other factors. Only 2 or 3 of these patients are improving due to an effect attributable to Lotronex.

[Slide]

These are the data from the second major efficacy study, study 3002. Again, we see very similar results. We have a placebo effect or spontaneous improvement effect ranging between 40 and 47 percent. If we look at the effect attributable to Lotronex, it is only 19 percent at month 1; 12 percent at month 2; and approximately 16 percent at month 3. Again, we see very similar numbers in terms of

the percentage of those who improve who have an effect attributable to Lotronex, only 2 or 3 of those patients out of 10.

[Slide]

What conclusions do we draw from this? Of women with diarrhea-predominant IBS who take Lotronex and improve, between 68 and 80 percent improve spontaneously or due to other factors not attributable to Lotronex. Many of these patients may continue to take Lotronex because of a false belief that improvement is due to a drug when, in fact, improvement is probably due to other factors.

[Slide]

These patients are exposed, possibly chronically because they believe that they are experiencing a drug benefit, to risks of the drug without benefit from the drug.

So, questions that we would like to pose before the advisory committee's perspectives on terminating treatments in patients who fail to respond to Lotronex, and how such patients can be identified.

Similarly, we would be interested in identifying specific conditions that should be met before the drug is used on a long-term basis. Are there ways by which responders can be identified, or are there things that the sponsor could do to identify such responders?

[Slide]

The overall conclusions about the benefit are that Lotronex is a palliative, not curative, treatment for IBS. Lotronex has not been shown to prevent progression of IBS symptoms. The proportion of women who have benefit attributable to Lotronex is modest.

One point which is not made on that slide is that in the two phase III studies women with severe abdominal pain and discomfort were specifically excluded from the study. Therefore, the effects of Lotronex in women who have the most severe abdominal pain and discomfort is not known simply because there is not data because those patients were excluded from the phase III studies. Because it is not on the slide, I will say that again -- women with severe abdominal pain or discomfort were excluded from the phase III study. Therefore, we do not have data on the patients who are most severely affected with abdominal pain and discomfort.

[Slide]

The administration of Lotronex only to target population would help optimize the benefit-risk ratio for the drug. Finally, administration of Lotronex only to true responders would help optimize the benefit-risk ratio. We would be interested in the advisory committee's input on these issues.

I will now turn the podium over to Dr. Hugo Gallo-

Torres who will discuss Lotronex and serious adverse events of the gastrointestinal tract.

Serious Adverse Events of the Gastrointestinal Tract

[Slide]

DR. GALLO-TORRES: Dr. Hanauer, members and guests of the advisory committee, ladies and gentlemen, I am going to briefly summarize Lotronex-associated serious adverse events of the GI tract.

[Slide]

This is a summary of the type of events that we have seen. The type of events can be categorized under colonopathies or hepatotoxicity. The colonopathies have been either constipation associated or ischemic colitis. So, we have one, two and three categories. There were no cases of constipation-associated colonopathies before approval. There were 4 cases of ischemic colitis and 1 of hepatotoxicity, for a total of 5 hospitalizations pre-approval.

There have been 7 cases of constipation associated, 8 of ischemic colitis and 2 additional cases of hepatotoxicity post-approval, for a total of 7 constipation associated, 12 ischemic colitis, 19 total colonopathies and 3 cases of hepatotoxicity.

[Slide]

These 7, 12 and 3 are reproduced again here. Of

the 7, 6 have required hospitalization. Of these 12, ischemic colitis cases, 8 have required hospitalization, and of these 3, 2 have required hospitalization, for a total of 16 cases that have required hospitalization up to June 1, the cut-off time for this particular set of data. Of the 6 constipation-associated cases, 3 have required surgery up to June 1. No case of ischemic colitis has required surgery. We asked Dr. Mangel to refer to this new case that he summarized for you because we believe that is the first case of ischemic colitis that has required surgery.

[Slide]

Again going to hepatotoxicity, there were 3 serious adverse events, 2 post-approval, 1 before approval, and 2 have required hospitalization. I am going to refer to every one of these three cases very briefly.

[Slide]

I am going to refer to patient 1, patient 2 and patient 3. All 3 patients were females. This one was 33 years old; this, 75 years old; and this, 80 years old. The adverse event in this patient occurred 22 days after initiation of therapy; this patient, on the first day; and this patient, 35 days after the beginning of the therapy. One important point I would like to make is that all these patients were on co-medications. All three patients were receiving multiple medications.

[Slide]

Again referring to patient 1, 2 and 3, and very briefly referring to the symptoms and signs that these patients had, this particular patient had depression and was overweight. The second patient had congestive heart failure, ascites, COPD and renal failure. We do not know what signs and symptoms patient 3 had.

What did the abnormal laboratory tests consist of? They all consisted of elevations in liver function tests. Specifically, transaminases, ALT, AST, alkaline phosphatase in all 3 cases and elevation of bilirubin in the first patient that was described in detail in the first advisory committee on alosetron.

Upon discontinuation of the medications in patient 1 and patient 3 all liver function tests became normal. We have no idea what happened to the liver function tests for patient 2 upon the challenge.

[Slide]

Turning to the colonopathies, specifically to ischemic colitis again, there was a total of 12 serious adverse events, 4 occurring pre- and 8 post-approval, and 8 of these 12 required hospitalization and I referred to 1 case of surgery before.

[Slide]

There is no such thing as representative or

typical case of ischemic colitis, from what we have heard this morning. These cases, especially the ones from the spontaneous reporting system, are by definition incomplete but I chose these cases to make a few points.

This is a patient, a 53-year old female who had diarrhea-type IBS. She had history of diverticular disease, and one of the first points I want to make is that several patients have been shown to have diverticular disease. This particular patient was put on this antibiotic for suspected diverticulitis and, indeed, if we look at all the cases of ischemic colitis there have been co-medications such as ERT, estrogen replacement therapy, and at least in one case imetrex, and these two medications, as mentioned by Dr. Wolfe this morning, have been associated with ischemic colitis.

The patient was treated with alosetron 1 mg b.i.d. for 2 days. She was hospitalized for 2-3 days because of rectal bleeding. Here is another point I would like to stress to you. All patients with ischemic colitis have experienced hematocetia, rectal bleeding. On CT, this patient had thickening of the splenic flexure, which was compatible with colitis or ischemic colitis and, again, up to the case described by Dr. Mangel this morning we have not seen the thumb-printing, the typical description of ischemic colitis in a textbook. Colonoscopy in this patient

confirmed ischemic colitis. And, this is one more point I would like to stress, this is the way to diagnosis ischemic colitis, by colonoscopy, and in this particular case the histopathology confirmed ischemic colitis.

So we were looking, more or less, for characteristics of these patients to look for risk factors, predisposing factors and so on.

[Slide]

In summary, we have under presentation and diagnostic criteria rectal bleeding that I mentioned before, hematocetia; abdominal pain; and bloody diarrhea. The duration of treatment at onset has been anywhere from 2 to 54 days. The abdominal CT scan has included mural thickening of varying degrees of severity in the small and the large bowel.

[Slide]

Colonoscopy has shown in the case of ischemic colitis patchy, friable, ischemic or hyperemic, edematous mucosa with erosions that later become necrotic, ulcerated and hemorrhagic with mucosal sloughing. The histopathological findings have consisted of mild edema of the lamina propria, focal coagulation necrosis of superficial crypts. So, up to the case described by Dr. Mangel, the lesion appears to be superficial. Indeed, normal architecture and spacing of deeper crypts have been

described. With this case, now I am not sure.

[Slide]

Turning to constipation-associated colonopathy, we have seen a total of 7. All of them occurred post-approval; no case pre-approval and 6 of the 7 have required hospitalization and 3 of these have required surgery.

[Slide]

Going through the same model that I applied before, I am going to talk very briefly about the 3 patients that required surgery, patient 1, patient 2 and patient 3. The 3 patients were female. This patient had alternating IBS. The serious adverse event in this patient happened 27 days after the initiation of therapy; this one, on the second day; and in this patient, 17 days -- the slide is wrong. It is 17 days, not 7 days.

The specific symptoms and signs in these patients were cramping, abdominal pain, fecal impaction, nausea and vomiting. In this patient, abdominal pain, fecal impaction and distention. And, abdominal pain, fever and peritoneal signs in the third patient.

[Slide]

The specific complications consisted of perforation of the sigmoid colon. It was an abscess in this patient. Small bowel obstruction. There was also active colitis in patient 2, and toxic megacolon, gangrenous

colitis, and transmural ischemia in this patient who also had bacteremia as well as heart and renal failure.

[Slide]

The specific surgical procedure consisted of repair of the sigmoid colon perforation in this patient; temporary decompression and colostomy in patient 2; and total colectomy. This patient had the entire colon removed, and ileostomy.

[Slide]

Briefly summarizing constipation, there was 1 case of fecal impaction that did not require hospitalization, and this patient experienced abdominal pain and constipation.

[Slide]

There have been 3 cases of fecal impaction that were hospitalized but that did not require surgery. One patient had abdominal pain and constipation. The next had abdominal pain and small bowel obstruction. The third had abdominal pain, bowel obstruction. She also had a stercal ulcer in the distal transverse colon and ischemic ulceration.

[Slide]

Finally the three cases that needed surgery, that were hospitalized, of course, one because of small bowel obstruction that required temporary decompression. The second, perforation of the sigmoid colon that required

repair of the perforation. And, the third case that I mentioned to you, of toxic megacolon, gangrenous colitis and transmural ischemia that required total colectomy with ileostomy.

[Slide]

I would like to finish my brief presentation by reminding you that Lotronex is a good medication for IBS. Nevertheless, it is palliative; it is not curative. It is symptomatic, and it has not been shown to prevent progression of symptoms.

[Slide]

I would like to remind you further that irritable bowel syndrome is a functional gastrointestinal disorder whose natural history is not associated with life-threatening sequelae, progression to colonic organic disease. It is certainly not associated with ischemic colitis, and most certainly not associated with constipation that may require surgery.

That is all I have to say, Mr. Chairman.

Risk Management Options

[Slide]

DR. RACZKOWSKI: I would now like to review some risk management options that are available to both FDA and/or to Glaxo Wellcome in terms of the risk management program for Lotronex.

[Slide]

As is summarized in the briefing document, there are several risk management options for marketed drugs. These include labeling, communications and educational programs, advertising, packaging, restricted distribution and withdrawal. An additional item which is not included here, which has been alluded to by the sponsor, has to do with performing additional studies in order to understand risk factors and etiologies for various adverse events.

[Slide]

I will briefly run through these options. When we talk about labeling, we talk both about the label which is on the immediate container and the outer package -- that is the sticker that defines the identity of the product, the milligram or weight of the product, and those sorts of things, including expiration and stability. But primarily, I think what we will be focusing on in this advisory committee is information that is provided either to professionals or to patients. That can be in two forms, either as a package insert for prescription drugs, and those package inserts include both the professional labeling as well as the patient package insert. A new mechanism that we now have in order to communicate with patients are medication guides.

[Slide]

I will briefly discuss these items about the patient because Nancy Ostrove, who will be following me, will be discussing them in more detail. But the first two items, the patient package inserts and medication guides, are items that can be used to inform patients about the benefits and risks of the drug and how to recognize those risks, should they occur.

What a patient package insert is basically, and Lotronex currently does have a patient package insert appended to the labeling, is basically an extension of the professional labeling and it can be distributed to patients when the drug is dispensed, however, that is not required. Important information about the drug is communicated in lay language.

[Slide]

A medication guide, which Dr. Ostrove will talk about in some detail, is an information leaflet for patients. In contrast to patient package inserts, FDA can require a medication guide. This is a relatively new mechanism that we now have in order to inform the patients about the benefits and risks and important things to be aware of when they take drugs, and these must be distributed to patients when the drug is dispensed and they may be used with unit-of-use packaging to enforce distribution.

[Slide]

I would now like to turn to professional labeling. The professional labeling for Lotronex, the sections that we have been working with Glaxo Wellcome on in terms of improving the risk management for this drug include the indications and usage section, the contraindications section, warning section, precautions, adverse events and the patient package insert.

[Slide]

Warnings sections describe serious adverse reactions and potential safety hazards. They also describe limitations in use imposed by serious adverse reactions, and they describe steps that should be taken if serious adverse reactions occur.

[Slide]

In order to qualify as a warning, there is only need for reasonable evidence of an association of a serious hazard with a drug. A causal relationship need not have been proved.

[Slide]

Boxed warnings are one mechanism, and a primary mechanism by which the prominence of a warning can be increased, particularly to healthcare providers. Boxed warnings refer to special problems, particularly those that may lead to death or serious injury, and these can be required by FDA and they are ordinarily based on clinical

data.

[Slide]

However, they may also be based on serious animal toxicity and, in general, the specific frequency of serious adverse reactions and, if known, approximate mortality and morbidity rates are included in boxed warnings.

The principal consequence of a boxed warning on advertising is that there are no reminder ads. Dr. Ostrove will be able to talk a bit more about what reminder ads are. Basically, those are ads in which simply the name of the product appears, for example, on a pen without any additional safety or efficacy information about the drug.

[Slide]

Well, how are boxed warnings used? This gets to the issue of when does FDA make a determination about when to request or impose a boxed warning. There are two major criteria. One is when there is an adverse reaction that is serious in proportion to the potential benefit or, when the benefit-risk should be considered before a drug is prescribed. For example, the physician and patient together may choose to either put the patient on alternative medication, or not to use the medication, or to put the patient on the medication before the drug is prescribed.

[Slide]

How are they used? Well, serious adverse

reactions that are preventable or decreased in frequency or severity by appropriate patient selection, for example, are often included as boxed warnings. Or, if careful monitoring is required, and example of this might be liver function tests to monitor for hepatotoxicity. Or, if there is a need to avoid certain concomitant therapy, or the specific need to avoid using the drug in a specific clinical situation.

[Slide]

They are also sometimes used for contraindicated situations or just to communicate important risk-benefit information about a drug. An example of this is when a drug is the only one in a class to have a particular risk that makes it inappropriate for first-line therapy.

We do have some preliminary data on some comparative agents that are used in the treatment of irritable bowel syndrome with drugs such as Imodium, Pepto Bismal, Lomotil and opium. For Pepto Bismal, Lomotil and opium, in the last roughly 25 or 30 years, there have been, according to our preliminary reports, less than a handful of adverse events reported as constipation. Constipation for Imodium, in contrast -- our preliminary reports indicate that there are several hundred reports of constipation. However, only seven of these have resulted in hospitalization. Again, this goes back to 1977.

[Slide]

So, the question has arisen should Lotronex have a black box, and the sponsor had requested the opportunity to discuss black boxes at this advisory committee. Well, with constipation there is a clear causal relationship of Lotronex with this adverse event. It is a dose-related side effect that occurred in 25-30 percent of patients who received Lotronex in clinical trials. About 10 percent of patients who took Lotronex in clinical trials had to discontinue the drug permanently because they could not tolerate it.

As Dr. Gallo-Torres has summarized, we have seen constipation reported as a serious adverse event now in 7 patients taking Lotronex, and 6 of these patients have been hospitalized and 3 underwent surgery.

[Slide]

Another possibility is a boxed warning for ischemic colitis. Again, in the initial clinical trial database the causal relationship to Lotronex was suggested but it was unclear. There were only 4 cases of ischemic colitis that were reported prior to approval. However, since approval, and using the cut-off date of June 1, 2000, we have seen an additional 8 reports, for a total of 12 reports and we believe, because of the frequency of these adverse event reports and a lack of other explaining factors, that there is a causal relationship to Lotronex.

FDA is also concerned about the lack of serious sequelae from ischemic colitis. So far, none has resulted in colectomy or death but we question whether that is a reassuring finding at this point, that none of these cases of ischemic colitis has gone on to more serious complications.

[Slide]

So constipation, again, has a clear causal relationship with Lotronex. I think I have summarized these data before -- 7 patients taking the drug, 6 patients were hospitalized, 3 underwent surgery. These were serious adverse event reports.

[Slide]

Additional risk-management tools that can be used are communication and educational programs. There are a number of options that can be used either by the FDA and/or the sponsor. These include "dear healthcare practitioner" letters and mailings by the sponsor, press releases, talk papers which is something that the FDA does, or health advisories to communicate serious health risks.

[Slide]

It is important to remember that communications should be geared not only to healthcare practitioners but also to consumers. And, educational programs by sponsors can be directed to healthcare practitioners to ensure the

optimal prescribing and implementation of necessary precautions.

[Slide]

Other options include educational programs by sponsors for the public or patients through toll-free numbers, Internet sites, newsletters and collaborative efforts with patient advocacy groups, and also in sales force outreach. I do believe that the sponsor has presented several of these.

[Slide]

In addition, advertising can be modified as part of the risk management program. Advertising can be restricted to general type in order to ensure that the drug is prescribed by physicians who are most experienced in the disease entity or the use of those types of drugs, and there can also be a voluntary restriction of direct to consumer advertising. In general, advertising must present a brief, accurate and balanced representation of adverse reactions, contraindications and effectiveness. As a reminder, reminder adds that call attention to the name of the drug only are not permitted for drugs with a boxed warning.

Another option for risk management is packaging options and restricted distribution. With packaging, for example, unit for dose packaging can be coupled with a medication guide or with the patient package insert to

ensure that the patient or consumer receives the information that is intended.

Restricted distribution is a mechanism that can ensure safer use and availability of drug of benefit over existing treatments to treat serious or life-threatening conditions. These can either be voluntary or in some circumstances they can be required by FDA. They only can be required by FDA when it is for an existing treatment to treat a serious or life-threatening condition. They cannot be required by FDA when it is not a serious or life-threatening conditions. However, this mechanism could be used, for example, to target a drug toward specific physicians who have experience with either diagnosis or irritable bowel syndrome or the diagnosis and management of some of these complications, such as constipation or ischemic colitis.

[Slide]

Finally, the ultimate risk management tool is cessation of marketing, which could be either voluntary withdrawal by the sponsor or withdrawal initiated by the FDA after approval because of an imminent hazard.

[Slide]

So, in conclusion, there are many options available to help manage risks for Lotronex, and we would be interested in hearing which interventions should be

considered.

[Slide]

As is further detailed in the questions, we would like to hear from the advisory committee and guests which risk management tool should be used for Lotronex and, importantly, to specify next steps if goals of a risk management program for Lotronex are not being realized. For example, simple education about a particular risk of a drug to either physicians or patients may not translate into altered prescribing patterns by that physician or to altered behaviors by the patient. Therefore, we are looking for some sort of assurance that education and outreach is associated with some sort of tangible change in behavior. We would also like some discussion on when should specific risk management tools be implemented -- what sort of thresholds should be used.

Thank you very much. I will now turn the podium over to Nancy Ostrove who will discuss medication guides and patient package inserts.

DR. HANAUER: Thank you, Dr. Raczkowski. Just for the committee and guests, those are ultimate questions that we are going to handle this afternoon. For the purpose of our subsequent discussions this morning, what I want to do is focus questions regarding those questions rather than how we are going to address those. I don't want to address

those specific questions right now, but if you have questions eventually about that, that is certainly fine.

Medication Guides

DR. OSTROVE: Good afternoon, ladies and gentlemen of the committee and the public.

[Slide]

I want to go into this pretty rapidly and briefly. Basically, in order to best understand the reason for use of medication guides as a risk management option, I think it is useful to have a sense of the variety of written information that patients can bet with their prescriptions. And, this is all understanding that in all cases the written information is intended to reenforce and supplement oral counseling that is given to the patient by the healthcare professional. It is not meant to stand on its own.

[Slide]

So, with that in mind, the first type of information I would like to just talk about very briefly, and the first type of information that is being distributed is in concert with a large-scale private sector effort that is guided by congressionally mandated goals for distributing useful written information to patients with their prescription products.

Now, this is information that is not produced by the sponsor or approved by FDA. It is supplied to

pharmacies by independent information providers. Again, they are not affiliated with the sponsors. It is generally computer generated at the point of purchase so that, for instance, in many cases you will see a piece of paper that is stapled to the bag the prescription comes in.

The distribution is fairly wide, at least in terms of an assessment that we recently did, but the concern that came up in the recent assessment showed that there is some improvement needed in the quality of information, specifically in specific types of information that are supposed to be in there according to the private sector program and risk disclosure is a big problem so far.

[Slide]

The other type of information I am going to talk about today can basically be called FDA approved patient labeling, as opposed to the first type. In this case, the sponsor drafts information; the FDA approves it after negotiating with the manufacturer. Now, the first type is basically patient package inserts or patient labeling that is required by regulations for specific products. Because the regulations are different, there are different format and content requirements. The ones that are best known are patient labeling for oral contraceptives and patient labeling for estrogen replacement therapy. This labeling is required to be distributed to patients, however, there are

questions that still remain about whether that distribution requirement is being achieved. A study that FDA did a number of years ago showed that, for instance, for required patient labeling for estrogen replacement therapy that was not in unit of use packaging about a fifth of the patients actually got it. I can speak from personal experience and can attest to the fact that many women are still not getting that information. However, when it is in unit of use labeling the patients tend to get it, although there are certain situations when even then the information is taken out of the unit of use.

The second type of patient prescription drug information FDA approved labeling we kind of refer to as voluntary patient labeling. Again, this is a case where the sponsor drafts the information and the FDA negotiates with the sponsor about the wording and then approves it. There is generally no uniformity in the format or the content. So, if the patient gets it they wouldn't know, just by looking at the format, that this is in fact a piece of FDA approved labeling. There is also no clear agreement within the agency as to whether distribution is actually required in terms of a legal requirement. The anecdotal evidence that we have indicates that distribution is spotty and, again, especially when it is not packaged in unit dose containers.

[Slide]

This brings us to new patient prescription drug labeling which we call medication guides. Similar to the others, this is information that the sponsor would draft and FDA would approve. It is a regulation, however, that it is not product specific as the other required labeling is. It is designed for outpatient products that pose a serious and significant public health concern for which the patient labeling is needed for safe and effective use by the patients. On average, our expectation is that this type of labeling would be used for between about five and ten products annually. It also requires that the information be distributed.

[Slide]

The circumstances that might trigger the need for a medication guide and for the FDA to basically tell the sponsor that this is a product that needs a medication guide are one of three: In one case you have, for instance, where the patient labeling could help prevent serious adverse effects. If you look at Lotronex as an example, the labeling, for instance, could be focused on patients recognizing the signs of bloody stools, worsening abdominal pain and constipation, and then told directly to stop taking the product and contact their doctor immediately.

A second triggering circumstance would be when a

patient needs to know of serious risks relative to the benefits of the product that might affect their decision to use the product or continue to use the product. Again, looking at the case of Lotronex, as we heard previously from Dr. Gallo-Torres and from Dr. Raczkowski, it is a symptomatic treatment. It is not curative. It has modest benefits. It doesn't affect the progression of the disease and, yet, it has some serious problems associated with it.

For the third triggering circumstance, that is when the drug is important to health and patient adherence to directions is critical to effective. Basically, what we are looking at here is products that affect serious clinical outcomes where the efficacy is hard to determine empirically but is highly dependent on proper administration. So, for instance, if a product needs to be taken on an empty stomach and you can't take anything to eat or drink for a period of time, or needs to be taken in some other specialized fashion, that is when this particular triggering circumstance is likely to operate.

[Slide]

Now, if the FDA determined that a product needs a medication guide, there are certain requirements that are written into the regulations that the guide has to be consistent with. It needs to be written in non-technical and understandable language. What we are talking about here

is that the language needs to be as simple as possible and needs to be understood by the end user, which is the patient in this particular instance.

It can't be promotional in tone or content. It needs to be scientifically accurate. It needs to be based on and consistent with professional labeling but, consistent with that first bullet, it doesn't have to have language that is identical to professional labeling because we know that in most cases that means it is not going to be understood by the consumer.

[Slide]

It also needs to be specific and comprehensive. Research has pretty consistently shown that it is not helpful to simply disclose general risks of a particular product, and it isn't especially helpful to disclose directions without the reasons for why those instructions or directions are important. You need to give people the rationale for what happens if they don't follow the directions. So, this "specific and comprehensive" gets at that issue.

It needs to be at least ten point minimum type size, legible and clearly presented where, for instance, the regulation talked about the appropriate use of highlighting techniques like bolding or underlining or the use of white space to emphasize specific portions of the text.

[Slide]

The regulation includes specifics about the headings that would be included in a medication guide. The first one, and the one that is really most important from the perspective of the patient is what is the most important information I should know about this product? This section includes a description of the public health concern that creates the medical guide need. So, if the patient doesn't read any further than this particular section, they get the information they need because it is right there, up at the beginning.

Following that there is information about, for instance, the discussion of disease and the benefits of treating the condition under what is the product. Then a discussion of the contraindications and what to do if those contraindications apply under who should not take the product. And, clearly, there might be some reference back to what is the most important information I should know.

[Slide]

How should I take is instructions for possible use. What should I avoid while taking the drug? That is basically the place to have specific important instructions to the patient that would ensure proper use. So, those are things you should avoid, activities -- being out in the sun without sun screen; substances to avoid; risks to mothers,

fetuses, nursing infants, children, geriatric patients etc. Then, finally what are the possible or reasonably likely side effects of the product?

[Slide]

I think it is absolutely critical, and I can't emphasize enough the fact that the law, the medication guide rule, requires that distribution is made, that the patient gets it. The manufacturer is responsible for ensuring distribution by one of two means, either providing enough of the medication guides to dispensers to give one to each patient, or providing the means to produce enough of these so that a patient can get it. The distributors and the regulation are responsible for passing on the medication guide. There is a notation on the container label that is required to be there to let the dispenser know that a medication guide is available and to let them know where it is available, specifically how they have it so that they can give it out to the patient. Again, in the regulation, the authorized dispenser is required to give it out.

[Slide]

FDA can exempt any applicant from any requirement of the medication guide regulations -- so, we leave some flexibility in there, except for consistency with the labeling and the title, that is, the medication guide title. There is another way that a patient might not get it, which

is that the prescriber can tell the dispenser not to give it out. If the prescriber believes that the information in the medication guide poses problems for a particular patient, a special concern, the prescriber can say don't give this patient the medication guide. However, this labeling is considered to be important enough that if the patient feels that they want information about the product the patient can override the physician's withholding request.

[Slide]

That was very quick but in conclusion, medication guides are for products that pose a serious and significant public health concern. They provide a uniform format and content so that patients have an easier time finding the information, and they put the important information up front, and medication guides are required to be distributed to patients.

With that, if you have any questions --

DR. HANAUER: One question. Could you just give us examples of drugs where medication guides have been required?

DR. OSTROVE: That is a good question. Actually, what I meant to say is that this rule was just put into effect in 1999. Currently, there are no official medication guides. There are no products that have official medication guides.

DR. HANAUER: Are there any that are under consideration besides this one?

DR. OSTROVE: Yes, there are but I can't say at this point what they are.

DR. RACZKOWSKI: I would just like to make an additional comment about medication guides. As Dr. Ostrove said, the FDA's anticipation is that there will be about five or ten drugs per year that will get medication guides. FDA recognizes that labeling has limitations and, therefore, risk management has to encompass other items in order to be effective. So, here to discuss postmarketing drug safety and risk intervention studies is Dr. Evelyn Rodriguez.

Postmarketing Drug Safety and Risk Intervention Studies

DR. RODRIGUEZ: Thank you. Since I am the last speaker before lunch, I will try to turn on my New York speed and go through this very quickly.

[Slide]

Today I am going to talk about postmarketing drug safety and risk intervention studies, and I am going to illustrate two risk intervention studies. I will review the labeling history for each of the two drugs that I am going to be discussing and I will review the study objective, methods, results and conclusions. I will then finish up with some broad summary and considerations for the advisory committee to consider and some future directions regarding

risk intervention.

[Slide]

I just want to review why we do postmarketing surveillance. There are limitations of phase III trials that are conducted in the NDA. Usually we enroll too few patients to answer a very simple question about specific efficacy for a specific indication. The patients are too median aged. That is, we usually don't study pediatric patients in the pivotal NDA trials and we usually don't enroll a lot of elderly patients.

The population is very narrow in that they have specific inclusion and exclusion criteria, and for Lotronex you heard that patients with more severe irritable bowel syndrome were eliminated from the NDA studies. And, they are too brief. They could last for several weeks, several months, certainly usually not more than a year and certainly not for years.

The population of users expands after drug approval. They expand in terms of age. They expand in terms of sex. In the case of Viagra, for example, we know that women use Viagra although it is not indicated. We also know that men have used Lotronex because we have received adverse event reports. Race/ethnicity issues are not usually addressed in the NDA and people of all races and ethnic groups take the drugs, and very little is known about

the use in pregnancy regarding drugs. In addition, there are a lot of rare events that by virtue of the limitations of the number of folks in NDA phase III studies you are not going to be able to detect. So, things that occur in 1/1000, 1/10,000 patients are not going to be detected in phase III trials.

[Slide]

How do we do postmarketing surveillance? We have a database reporting system called the adverse event reporting system, which is a computerized system that stores all of the voluntary reports that we receive from physicians and providers. It is a very cost effective method that is especially useful to generate signals for rare adverse events, and we currently receive about 250,000 reports per year.

[Slide]

I would like to review for you the factors that we use in looking at postmarketing causality assessment. We look at the temporal relationship of the drug to the adverse events. We look at the biological plausibility that the drug can cause the event. Any known class effect, of course, we take into consideration if this is another drug in a class of drugs. For example, for the fluoroquinolones we are very careful about QT prolongation among the whole class of drugs. So, that is something we look at very

closely. Any previous premarketing findings in the phase III studies. For example, Lotronex constipation and ischemic colitis we were particularly concerned about. And, anything that looked like it had a dose-related effect.

[Slide]

With regard to the temporal association, we look at the onset time and progression of the adverse event very carefully. We look for confirmation of a diagnosis. When the drug is discontinued, do we see dechallenge? That is, does the adverse reaction then go away? Upon restarting the drug, do we see a rechallenge phenomenon? That is, upon restarting the drug do we see the adverse event again recurring? We look at any underlying diseases that may contribute or may give rise to the alleged adverse event that is reported to us, and we look at any concomitant drugs that could confound or can contribute or can actually be the underlying reason.

[Slide]

So, how do we use cases identified in AERS? Well, we develop a case definition, and we either use the reporter's initial clinical diagnosis or we use one from the literature. Then, we develop a case series using these reports. Now, these reports in AERS are not developed into cases. We have to, by hand, sort of double-check that these are reports are not duplicative. So we develop specific

cases and sort of collate all of the reports for each one of the cases. We do a careful causality assessment, as I described. We look at conditions of exposure. Any risk factors and confounders are also noted.

[Slide]

There are substantial barriers to reporting which cause under-reporting. This is a voluntary system. The physician or provider needs to recognize that this could be an adverse event. He or she then needs to attribute the drug to the event, and establishing an adverse event to a drug is something that a provider may, indeed, wish to do although having a causality assessment before it is reported to the FDA is not required. We really would like to know about as many of these possible events -- it doesn't require a confirmatory diagnosis for us. We do that later upon evaluation. Labeled adverse events are less likely to be reported, and there are substantial constraints -- time constraints for providers, fear of litigation, desire by physicians and others to publish these interesting findings, and fearful that FDA will beat them to the journals, and privacy concerns are becoming really of increased concern to the public as well as to providers.

[Slide]

These are some estimates of under-reporting from the literature. You can see that they range from 0.3

percent for hospitalization for toxicity due to digitalis, a little bit less than 3 percent in the Rhode Island survey on serious adverse reactions, and Maryland's survey showed about 8-13 percent. So, it really spans the gamut. It is really individual to the drug, to the adverse reaction itself, and it is very hard to extrapolate for a given drug situation like this one.

[Slide]

With Lotronex we did have some premarketing cases of ischemic colitis and constipation, and in the postmarketing area we did have serious cases of ischemic colitis and serious complications of constipation very early in marketing, which we think is very notable. As Dr. Raczkowski had alluded to earlier, we did take a look at some of the other drugs that are used in IBS, and this really is a huge signal here.

[Slide]

Possible next steps for assessing the risk and the incidence -- actually, doing an incidence study for serious outcomes of ischemic colitis and constipation but it is going to be difficult to ascertain all of these cases in automated databases because the ICD-9 codes are non-specific. You have to cast a very wide net, and there would be substantial under-reporting for a diagnosis of constipation.

Risk factor identification is going to be very important, and may be feasible for ischemic colitis if complete ascertainment is assured, and the company themselves has alluded to the fact that they need to develop algorithms to identify IBS patients and constipation for all of these diagnoses. So, those algorithms still need to be developed and still need to be validated through medical record abstraction. Also, constipation as a risk factor for serious GI outcomes is going to be hard to evaluate because it is associated with irritable bowel syndrome which is the indication for the drug. So how do you tease out what came before, what came after and so forth? I think it is going to be very difficult to try to tease that out.

[Slide]

Other possible next steps -- implementing risk interventions, education, labeling changes and other things that the company and we have alluded to today, and evaluating whether the risk interventions are achieving the desired goals.

[Slide]

Now I would like to go through a couple of drug case histories and risk intervention studies associated with them.

[Slide]

The first case history deals with a drug that was

approved in January of '97, was launched two months later and seven months after marketing we received the first report of acute liver failure. After getting more reports of these adverse events of hepatotoxicity and acute liver failure, several re-labelings were done, several "dear doctor" letters were sent to practitioners that included recommendations for liver transaminase testing.

[Slide]

Our objective in this risk intervention study was to assess the impact of labeling changes regarding liver transaminase monitoring in a large managed care organization, using automated claims, again, using ICD-9 codes for diagnosis and CPT codes for liver transaminase monitoring.

[Slide]

The recommended liver transaminase monitoring did vary slightly with each labeling change, and the last labeling change that we were most interested in did recommend a baseline test, with monthly monitoring for the first eight months, and these data have been presented to a previous advisory committee.

[Slide]

The study was conducted in the United HealthGroup database and we assembled three separate cohorts. Cohort 1, which totaled 2307 patients, was assembled before the first

"dear doctor" letter in October of '97. Cohort 2 was assembled after the second "dear doctor" letter in December. Those totaled 2823 patients. And, after the third "dear doctor" letter in August, '98 the third cohort was assembled with about 1400 patients.

[Slide]

What we discovered was that liver transaminase monitoring at baseline by cohort occurred about 24 percent of the time in cohort 1, and then with subsequent cohorts improved to 45 percent with the third cohort.

[Slide]

This slide depicts the full compliance with monthly liver transaminase monitoring by cohort, cohorts 1, 2 and 3, among users of this particular drug. So, in cohort 1 only 2.6 percent of patients in month 1 received liver transaminase testing. In month 2, 0.8; in month 3, 0.3 percent. It improved slightly with each of the cohorts so that if you look across month 1 2.6 percent improved to 7.3 percent, which then improved to 9.3 percent in cohort 3. Nonetheless, if you follow it out to month 4 in cohort 3, only 0.5 percent of patients had liver transaminase testing as recommended by the label.

[Slide]

So in conclusion, there was poor compliance with full liver transaminase monitoring as recommended by

labeling, and there was better compliance with the baseline liver transaminase testing that improved with each labeling change to a maximum of only 45 percent.

[Slide]

These are some investigators who participated in that study.

[Slide]

I am going to present now the second drug history and risk intervention study regarding a drug that was approved in July of 1993.

[Slide]

We received the first reports of ventricular arrhythmia, which was a drug interaction with an antifungal drug, in December of 1994. There were multiple "dear healthcare practitioner" letters once more that described new contraindications and warnings for specific drugs and underlying medical conditions --

[Slide]

-- with black box warning for a contraindication for QT interval prolonging drugs, and cardiovascular and medical conditions, relegated to a second-line indication and "dear doctor" letter in June of 1998.

[Slide]

The study objective was to describe the impact of labeling changes through June of 1998, and the

contraindications were the cytochrome p450, 3A4 enzyme inhibitor drugs, QT prolonging drugs, and contraindicated co-morbidities.

[Slide]

In this study, instead of using a single database, we used three separate databases, sites A, B and C, and we looked at two distinct time period, before the "dear doctor' letter of June 1998, the year before, and then the year after the "dear doctor" letter.

[Slide]

We had three different sites with three different models of healthcare delivery, the first one being an IPA, the second one being a Medicaid managed care organization, and the third one being a consortium of HMOs.

[Slide]

These were the number of patients in each cohort by site that were available through June of '98, before the "dear doctor" letter of June of 1998 at each of the sites. We had about 17,000 in site A, about 4800 in site B and about 8000 in site C. These numbers varied slightly in the cohort afterwards. These were separate cross-sectional analyses.

[Slide]

These are the results for contraindicated drug or disease. Before the "dear doctor" letter at site A 29

percent of patients had underlying contraindicated drug or disease that were prescribed the drug, compared to 26 percent. In site B almost 60 percent. That decreased ever so slightly to 57 percent. In site C 29 percent versus 27 percent -- really not much of a change.

[Slide]

So, no reduction in use was really found after the labeling changes and "dear doctor" letter of June, 1998 with regard to the many contraindications in the label.

[Slide]

These are some of the investigators and sites that participated there.

[Slide]

In summary, and future considerations for the advisory committee, risk intervention studies are useful to assess the effect of labeling and "dear doctor" letters, and these two studies suggest labeling fatigue phenomenon. That is, with repeated labeling you really cannot accomplish much. It looks like providers and patients are confused and do not understand after multiple re-labelings what the really important message is. Other strategies, such as education targeting prescribers and patients, may be useful to encourage the implementation of recommended risk management efforts.

[Slide]

Future directions for us -- by "us" I mean industry, FDA and other agencies who would like to look at this further, we need to determine how prescribers interpret information from "dear doctor" letters and other educational materials that are given them. We need to still determine what the best format is to inform prescribers and patients of drug safety concerns -- is it the patient package insert? What kind of information do we need to put in a med. guide? Company sales materials and the utility of those materials, and perhaps even CME courses.

[Slide]

We need to determine how information, contraindications and monitoring recommendations are used by providers, and specifically with this drug what is the feasibility of constipation as a contraindication in labeling and in educational efforts.

[Slide]

We need to conduct risk intervention studies in multiple databases because, as I showed you in the second case example, it can vary by site and it may not look so bad, you know, in site A but when you look at site B -- well, you know, there may be some differences in population that may make labeling more challenging. And, it needs to reflect the different range of healthcare services delivery system, HMOs, Medicaid and so forth. Also, the findings

need to be validated in databases with medical record review.

That really is the end of my presentation right now. I am prepared to answer any questions later.

DR. HANAUER: Are you going to make conclusions?

[Slide]

DR. RACZKOWSKI: Three slides.

Summary of Issues

[Slide]

I would just like to summarize briefly some of the issues that FDA has identified. In terms of the benefit of Lotronex, number one, if a drug is not effective in a population taking the drug, those patients experience risk without benefit. Number two, if a drug is not effective in an individual taking a drug, for example, if the patient is a non-responder to that drug, that patient experiences risk without benefit.

[Slide]

Irritable bowel syndrome is a functional gastrointestinal disorder, and the natural history of this disorder is not associated with life-threatening sequelae or progression to colonic organic disease such as ischemic colitis or constipation that may require surgery.

[Slide]

Lotronex treatment for IBS is a palliative, not

curative, treatment. It is a symptomatic treatment which was not shown to prevent progression of symptoms. Finally, as Dr. Rodriguez pointed out, labeling as a risk intervention is, by itself, not sufficient and needs to be coupled with other risk management interventions.

Thank you very much.

DR. HANAUER: Well, Dr. Raczkowski, you put us between a black box and a hard place.

[Laughter]

Are there questions from the committee for the agency? Dr. Wolfe?

DR. WOLFE: Dr. Raczkowski, you compared Lotronex to narcotics, which we generally try to avoid. Not only that, but people are not going to report constipation with narcotics. We expect it. And, there are serious sequelae from narcotics. I think a better comparison would be to glycocyamine or to other spasmolytic agents. Do you have any comparisons to those drugs?

DR. RACZKOWSKI: We don't have data at this time but we will be looking into it. We do believe the comparison needs to be made for the same indication because risk-benefit could differ by indication. So, in other words, if a drug is used for treatment of irritable bowel syndrome, that would be the best possible comparison that could be made.

DR. HANAUER: Dr. Blum?

DR. BLUM: Yes, first of all with narcotics, after running a methadone clinic for ten years, it is one 100 percent you get constipated, but I never reported it to anyone.

Another thing is that again, I want to come back to empowering the patient. We all talk about "dear doctor" letters, but how about a "dear patient" letter? You know, I sit on an IRB and when a patient comes in and enrolls in a study we tell him he is going to get three blood tests over this length of time, and you may get this, and if you get this symptom your doctor will do this, that and the other thing. Why can't that type of information, including blood tests to look for hepatotoxicity because there is no other way to do it -- whey can't that type of information be empowered to the patient so the patient knows what is going on, not just the physician, the nurse practitioner or PA?

DR. HANAUER: Dr. Laine?

DR. LAINE: It is actually more for the sponsor. We can wait until afterwards but it is a timing issue -- I mean, two issues related to the indications. One, I asked at the last meeting if the sponsor had any information on saying after a certain period of time who would or wouldn't respond. Looking at those curves, they flatten out and, especially given what we are doing today, is there any

information to say if somebody doesn't respond at two weeks, four weeks, three weeks, whatever, that that person should them no longer take the medication? So, I just bring that up again for the sponsor.

The second issue about timing is since the sponsor has suggested they want to have an even playing field, I notice that after yesterday's discussion we felt strongly that we should only give indications for the length of time of the trials. I notice looking through the package insert that there was not a time limit. In other words, it does not say up to 12 weeks. So, that is something else we should just consider revisiting.

DR. HANAUER: Yes, but I will take the corollary to that because with alosetron we had data after cessation of the drug demonstrating going back to baseline, whereas with the product yesterday there was no subsequent data and that is what I think drove some of the points of limitation.

DR. MANGEL: Dr. Hanauer, can I also give a clarification?

DR. HANAUER: We would love to hear your clarification.

DR. MANGEL: It actually does specify, Dr. Laine, in the clinical trial section of the label that the clinical trials were only for 12 weeks duration and, of course, once again, risk-benefit -- all of this is comparative. As

pointed out in the CMS-4 report, an agent such as Prozac, I believe the clinical studies are 6 weeks. You would not advocate that after 6 weeks of treatment with Prozac if your patient is doing well to discontinue Prozac treatment.

You know, we also feel that Pepto Bismal is not a relevant comparator. We also do know agents, like dicyclamine, agents like tricyclics -- there are absolutely reported sequelae of constipation. In the label for dicyclamine as either a precaution or a warning is the information about toxic megacolon.

We also need to remember that IBS is a multi-dimensional disorder. Alosetron produces multi-dimensional benefit. It is absolutely incorrect to represent the benefit of alosetron as a single percentage. If I could have slide B13?

[Slide]

We actually philosophically disagree with the way benefit is presented. These are numbers from the year 2000 PDR and I just want to extrapolate that same line of reasoning and this, in my opinion, is absolutely not the way physicians judge the benefit of medications. Zantac, a drug we believe is an excellent agent, for gastric ulcer --

[Laughter]

-- the healing rate on placebo, 51 percent, on Zantac, 68 percent. This represents a 17 percent

differential over placebo. Then you look at Prilosec, another excellent agent for control of acid suppression, 48 percent versus 75 percent, a differential of 27 percent. Thus, it would once again suggest that only 1/4 patients healed their ulcer. Paxil, a very good agent for treatment of depression, in their follow-up study 61 percent of placebo, 85 percent of active. This would suggest that only 1/4 patients are getting better.

DR. LAINE: I was wondering if you are able to answer the question I asked.

DR. MANGEL: Sure. In the 3001 study for adequate relief, significant benefit over placebo occurred from the fourth week of treatment and persisted. For urgency, consistency and frequency, in 3001 and 3002 benefit was achieved at the first week of treatment.

DR. HANAUER: But I think what he was asking is how do we know when they are not going to respond?

DR. MANGEL: Yes, and in discussions with the FDA, and you will see a proposal in the draft labeling, if patients feel they are not a responder after four weeks of treatment, the treatment should be discontinued. I think we are in agreement with the FDA that a four-week trial is suitable. If you don't have benefit by then, to discontinue.

DR. HANAUER: Dr. Raczkowski?

DR. RACZKOWSKI: I would just like a second to respond to Dr. Mangel's comment. I was very careful to say that the response rates represented the amount that is attributable to the drug as opposed to other causes. It does not imply that only 1/4 patients healed the ulcers. All the patients healed the ulcers, but whatever percentage is attributable to the drug is a relatively small percent.

DR. MANGEL: Yes, and my point, Dr. Raczkowski, is that I believe that is not the standard way that therapeutic advantage of medications is evaluated, and for the Lotronex example in particular, your numbers only referred to the single endpoint of adequate relief. It is a multi-dimensional disorder. Lotronex is producing multi-dimensional benefit. A single summary number does not satisfactorily represent the benefit.

DR. HANAUER: Dr. Welton?

DR. WELTON: I have a question that was raised by you Dr. Rodriguez. I have a concern that we have significant under-reporting of ischemic colitis even in these study patients because in one of these reams of papers we had numbers of patients who had flexible sigmoidoscopies showing just hemorrhoids but it was only a flex. sig. and a lot of these patients that we hear about actually have the disease at the splenic flexure. So, I guess the comment is if we are going to follow these patients along, I think it

requires more than a flex. sig. because I am afraid that we are only actually seeing seven patients reported but I think it may be even more.

DR. HANAUER: Any other questions from the committee or guests on these presentations before we take a break?

[No response]

We are going to start exactly at 1:30 with the open forum. Thanks.

[Whereupon, at 12:45 p.m., the proceedings were recessed until 1:30 p.m.]

AFTERNOON PROCEEDINGS

DR. HANAUER: I would welcome you back. We will now have comments. As you know, this is an open forum, however, I would like to preface this. The committee has heard background on the irritable bowel syndrome. We heard yesterday from Miss Norton about the impact of irritable bowel syndrome. The point of today's meeting is specifically to discuss the risk management of Lotronex, and I would hope that the speakers will limit their discussions to that, or they will be, not rudely but graciously, interrupted by me.

The first speaker is Dr. Richard Krause, I believe. We will ask the speakers, please, to disclose any financial remuneration for your attendance or sponsorship.

Open Public Hearing

DR. KRAUSE: Yes, I am Richard Krause, from Chattanooga, Tennessee, and my expenses are being paid by Glaxo. I am here as a patient advocate. I have been practicing for 23 years in GI practice, and for the last 10 years have been doing clinical research. For the last 5 years I have done studies on Lotronex, and I have 123 patients on our clinical research study, and probably close to 100 patients over the last 6 months have been given prescriptions.

So, I have a lot of experience and the only two

points I want to make are that I use Lotronex only when the patients have diarrhea to the point that I feel that it is disabling to their lifestyle. I also preface, when I give the patient the prescription, that there is a good possibility they are going to get constipation, and I go over with them how we treat the constipation.

I think that in listening to what has been going on this morning, the problem is that most of the patients, by the time they get back to their physician and tell them they are constipated, they are into almost a week of constipation and, in my mind, that is why they are having the complications. So, I put them on stool softeners. I tell them to take Milk of Magnesia if they haven't had a bowel movement in a few days. Then we use Mirolax to add to that. So, I think if I tell the patient ahead of time they are probably going to get constipated, they are not going to get into the major complications.

DR. HANAUER: Do you have any data that if you tell the patients ahead of time that they will not, or is this just what you think?

DR. KRAUSE: Well, we have actually two nurse practitioners and so we follow up, because in doing the research studies I know that my patients have gotten constipated. Of course, the patients in the study are the worst of the worst. So, I mean, they would rather be

constipated and be able to go out to dinner with their friends than not to be able to eat out at a restaurant. So, yes, we have feedback and we ask the patients to call back. So, I mean, I think it is working.

DR. HANAUER: So, the patients you put into the trial were those with severe symptoms?

DR. KRAUSE: Absolutely. But, of course, now we are getting a little more relaxed and so we are warning them ahead of time they are probably going to get constipated.

DR. HANAUER: Okay. That is interesting because the trials were for patients with mild to moderate symptoms but we appreciate your honesty.

DR. BLUM: Just one question, do you know how many of your patients have refills?

DR. KRAUSE: Have refills?

DR. BLUM: Have refilled their prescription, their initial prescription in the last three months?

DR. KRAUSE: I don't really know that data.

DR. HANAUER: The next speaker is Ms. Cook.

MS. COOK: Thank you for letting me be here, and thank you, Glaxo, for making me aware of this meeting. I hope, because I am from Alabama, that you will bear with me because I do talk a little slow. I am an administrative assistant for a physician's office. I have had irritable bowel syndrome for 15 years. I have had all the tests that

you can have and, by the way, I am not being compensated by Glaxo. I am here on my own.

I was treated by some of the best gastroenterologists over the last 15 years. Eight years ago I was diagnosed. I was told there was no cure, that I just had to learn to live with it. I have had MMI tests. I have seen several psychiatrists who tried to see if it was in my head, and it was not. I have missed a lot of work. My boss was very generous and let me work from home so that I could, you know, contribute to the office and do what I needed to do there.

I was on Lomotil two tablets four times a day. It did not work. In March of this year I was fortunate enough to be able to get Lotronex. After being on Lotronex, my life has changed drastically. Prior to Lotronex I was approved by the Social Security office for disability due to irritable bowel syndrome. In May of this year I called the office and told them that I no longer needed the disability. They still don't understand that. They want to know how I can do without Social Security benefits. I said I no longer qualify. So, they are real happy and they want to know what the name of this drug is. So, I have told them all about Lotronex --

[Laughter]

Without Lotronex my life was not a life. I did

not have a life. I went constantly with Depends. I lived with Depends. I carried them in my car; I carried them in my purse. I kept them on my body; I thought they were a second skin. I no longer have those. I now visit with my grandchildren. I go shopping. I didn't check here to see where the nearest bathroom was. I was able to fly on a plane here without worrying about whether I was going to be seated next to the lavatory.

My condition has improved drastically. I no longer have to depend on anything by Lotronex. I have a drug of choice -- it is Lotronex.

DR. HANAUER: Did anyone warn you about potential complications when you received the drug?

MS. COOK: Yes, the detail rep who came into my office did.

DR. HANAUER: The detail rep?

MS. COOK: The drug rep.

DR. HANAUER: The drug rep told you about it. What did your doctor tell you about it?

MS. COOK: My doctor that I work for -- he said I have a new drug on the market for irritable bowel syndrome. Do you have any patients? She said I have an employee.

DR. HANAUER: Did they ask what kind of irritable bowel syndrome you had?

MS. COOK: I had diarrhea seven days a week. I

knew what I had.

DR. HANAUER: And, did the drug rep warn you --

MS. COOK: I read the insert myself.

DR. HANAUER: You read the insert.

MS. COOK: I read the insert.

DR. HANAUER: Did the doctor discuss anything with you?

MS. COOK: I am an administrator of a doctor's office; the doctor did not have to discuss it with me. I read it all myself. My doctor and I have a good relationship.

DR. HANAUER: Thank you.

MS. COOK: You are welcome.

DR. HANAUER: Ms. Sandy Conner, please.

MS. CONNER: Hello. My name is Sandy Conner. Glaxo Wellcome did pay for my travel expenses but I am here on my own.

I have suffered from irritable bowel syndrome for about ten years. Over the years, I have also tried over-the-counter medicines as well as prescriptions to no avail. It is very hard when you have diarrhea every single day. Going to work was a struggle and there were times when I could be on the phone and actually hang up on the person I was talking to and run to the bathroom. Also, times going to the grocery store or shopping was a problem. I had

almost no social life at all. Even being in a restaurant, trying to order food and end up not eating and just going home. Trying to have a relationship is worse. I have two nieces that live about an hour's drive from me and it is very hard to even drive to see them.

With IBS, it does come on with no warning. So, after many discussions with my doctor, he put me in a clinical research study for three months. At that point, that was definitely the best decision to take this medicine, Lotronex. My diarrhea seemed to be under control after a few weeks. I was actually starting to be able to do normal, everyday things, and I really felt better. When the clinical study ended after the three months I could continue on in the one-year study. This was the best year of my life. I was able to go skiing or work out and actually enjoyed going to the basketball games.

Just when I was starting to enjoy my life again, the clinical study ended. I was just about to go on vacation when I received the news. I was flying to Florida to visit my dad. I had tried everything to get my doctor to give me more medicine but he couldn't. He said they were waiting to get approval from the Food and Drug Administration and that can take a while.

I was devastated, as I sat in my doctor's office in tears. I was really doing so good. But I patiently

waited for Lotronex to go on the market. It has been about a year now and Lotronex was recently approved, and I was finally able to get the prescription. I have been taking it twice a day for about three months. My life has been pretty normal lately. I attended a final women's basketball game in Philadelphia, and recently I was promoted to executive secretary for the assistant superintendent of schools. Without Lotronex, I truly believe none of these things would have happened. With Lotronex I have control over my IBS and my IBS does not control me. Thank you.

DR. HANAUER: I am going to ask you the same simple questions. The questions are, did anyone tell you that there might be a risk to this medication, not when you were in the trial but once it was approved?

MS. CONNER: Yes, the side effects?

DR. HANAUER: Yes.

MS. CONNER: Yes. I have no constipation.

DR. HANAUER: No, but who told you that there might be side effects?

MS. CONNER: My doctor.

DR. HANAUER: Okay. Did your pharmacist say anything?

MS. CONNER: No, I did a mail order prescription for three months.

DR. HANAUER: Thank you.

MS. CONNER: Thank you.

DR. HANAUER: Miss Norton? Nancy Norton again.

MS. NORTON: Thank you, members of the committee. I hope you are not going to be tired of hearing from me once again today but I am here today to speak about the serious nature of IBS and the disconnect that still exists between the perceptions of the disease and the actual experience, and the profound impact this disease can have on the lives of those who suffer from it.

Perhaps because there is a general association of IBS with life stress and the assumption that it doesn't kill you, the disorder has historically been marginalized, symptoms trivialized, and patients dismissed as more in need of psychological treatment than medical care. Forty million Americans are thankful that IBS is not a killer disease, but that is not to say that IBS is not a serious disease. IBS doesn't kill. Rather, it robs people of their life.

As the founder of IFFGD, I began the organization with the intent of raising awareness. I can assure you that in 1991, when we began the organization, little information was available to patients. Unfortunately, there still persists an attitude by many in the medical community that IBS is something that need not be taken seriously.

It has only been recently that investigators and practitioners have begun to appreciate that a functional GI

disorder such as IBS is a chronic medical condition with central and peripheral pathophysiology, involving a complex interaction of multiple mechanisms, a disregulation of brain-gut systems. We now have more diagnostic tools to look at dysfunction. In addition to traditional motility tests, we have the Rome criteria that facilitate a symptom-based diagnosis. We have barostats that measure intestinal tone, and we even have brain imaging that allows us to see how patterns of neural function differ in patients with IBS.

We have entered an era where we can make a positive diagnosis of IBS based on the Rome criteria, along with limited tests to rule out other disease factors, rather than a negative diagnosis based solely on exclusion of other possible inflammatory, infectious or structural abnormalities. Yet, in the recent survey, IBS in American Women, when physicians were asked about their familiarity with the Rome criteria only 1 percent of primary care physicians were very familiar with it, and 14 percent were somewhat familiar with it. In the GI community 18 percent of gastroenterologists were familiar with it, and 41 percent were somewhat familiar with the Rome criteria.

Thus, there is a failure within the medical community to make available to patients a safe, consistent and supportive means of diagnosing IBS in treating the disease. An affirmative diagnosis of IBS facilitates a

positive patient and physician relationship in which a treatment approach can be formulated which often includes a combination of treatment modalities that is best suited to the individual patient. Those patients who do not receive an affirmative diagnosis may be asked to endure an array of progressively invasive tests, only to receive in the end a diagnosis that begins with the words, "there is nothing wrong with you," and perhaps further, "let's try to treat the single symptom," knowing full-well that IBS is characterized by multiple symptoms, leaving the patient to still contend with either the pain, the diarrhea, the constipation, the bloating, the gas, the urgency and perhaps the fecal soiling.

At IFFGD we are contacted every single day of the year by people who come to us, seeking help like refugees from this type of negative clinical experience. It is important to understand that IBS is a complex disease entity with potentially serious and even devastating consequences for the millions who suffer from it. Does the benchmark for burden of illness need to be equated to cancer before we consider a disease to be serious enough to provide medical management and potential drug therapy? I certainly hope not for IBS is a disease that we need to take seriously and ease the toll of human suffering.

We have data that shows us the effect on quality

of life, and we also have data that demonstrates the economic impact of IBS increased absenteeism, increases in annual healthcare bills and perhaps unnecessary surgery. All of this, again, confirms a pattern of human suffering. The data is there in concrete terms for those who need to see it to believe it.

For the IBS patient who lives it, it is quite a different matter. The person who lives with IBS is continually making adjustments in their life to accommodate the symptoms they experience. Little by little we begin to shut ourselves off from society and family because of our symptoms. IBS can be a very isolating condition. It is difficult to express the loss that those of us feel for months and years of living with IBS. Symptoms may range from mild to severe, from inconvenient to devastating. For some people, they may question whether to eat that hot spicy food they crave; for others it is the question of do they eat at all. There is a common expression among us, "nothing in; nothing out." Depending on what commitments a person has for the day or the week, they try to juggle this complicated guessing game of what to eat, what to drink, what medications to take, their sleep patterns, their stress management techniques, and all of this often to no avail.

We have recognized IBS as a chronic disease. We are making progress but a recent article in the British

Medical Journal made the observation that classically only half of patients with chronic disease are identified. Only half of those identified receive treatment, and only half of those treated are treated adequately, meaning that only 12 percent are being optimally managed. I would ask that we move forward in offering patients the best possible care. The responsibility is a shared on, beginning in medical school and carried through to the practicing physicians. The pharmaceutical companies also share in the responsibility of educating the medical community and the general public about the risks and the benefits of any medication.

Last but not least, we, the patients, share in the responsibility of educating ourselves about any medical condition and medications we are taking. Our goals have been to raise awareness and provide educational information and support to those who suffer from functional GI disorders. At IFFGD, we have been fortunate to be part of a community of scientists and clinicians who share our concerns and believe in the needs of these patients. I hope that we will all continue this effect to improve the lives of IBS patients. Thank you.

DR. HANAUER: Thank you.

Discussion and Questions

We have a lot to go over in the next period of

time. So, I will try, as best I can, to moderate the time frame related to where we are at in the questions. So, I am going to take it from the very beginning of our charge, which is to look at goals and outcomes of risk management -- well, actually we have four charges which are, number one, to look at goals and outcomes of risk management plan for Lotronex. Number two, what are the interventions that we would advise in that program? Number three, how to assess the impact of the interventions? And, number four, God forbid the impact doesn't work, what would be the next plans?

So to begin with, the first question that we are charged with is to discuss the specific safety goals and outcomes that the committee would like to see through implementation of a risk management program for Lotronex. And, we are going to go through the specific examples. The first is, should there be dissemination of the current safety information about Lotronex? Should that be disseminated? Is there any dissent that it shouldn't be?

[No response]

So, then the question is we do have updated safety information about Lotronex, who should it be disseminated to? What are the priorities according to this committee? And, the options include the whole list that we have seen from the physicians to the pharmacists, to patients, family

members.

DR. LAINE: It struck me that the sponsor and everybody else agrees that the whole gamut was reasonable. So, I don't see any downside so I would say that whole list.

DR. HANAUER: Any dissent to that? Everybody should hear it? The entire tree. Is that clear?

[No response]

The next question is a goal should be to assure that patients at high risk for toxicities of Lotronex are not treated with the drug. If so, how are these patients to be identified? I guess I would ask the committee are you able to ascertain from the data that we have been given who is at high risk for complications? Your silence says no.

DR. AVORN: Well, clearly preexisting constipation and other obvious things have come up, and those are obviously important. But I was struck this morning with the need for a lot more data, which I assume Glaxo is going to be collecting, on the risk factors -- in a really rigorous epidemiologic sense -- that would make it more possible in the future to predict who is at increased risk beyond just history of constipation and other obvious things. I am pleased to hear that that is going to be identified in the course of the next months to years by Glaxo and their collaborators.

DR. HANAUER: Yes, Dr. Wolfe?

DR. WOLFE: In addition to the risks for developing constipation, obviously the preexisting constipation, we mentioned the possibility of identifying those at risk for non-occlusive disease by people who had been smokers or taking birth control pills. They may be at increased risk but, again, the numbers are very, very small.

DR. HANAUER: Do you believe you have evidence to say that those people are at increased risk?

DR. WOLFE: The only evidence is of the seven cases we looked at, four of the seven were taking estrogens or birth control pills.

DR. HANAUER: So, what do you want to do about that?

DR. WOLFE: If we are adding risk -- again, this is a situation, in a way, until proven otherwise where when we identify possible risk factors they should be identified. Again, you have definite and possible and this is a possible risk. First of all, we know that people who smoke and take birth control pills are at increased risk for developing thrombotic events, and here is a situation where it looks like it may be a possibility and that is something that needs to be investigated but do we wait until the proof is there before we tell people to stop smoking?

DR. WELTON: But do we know this is a thrombotic event? I have no data that says this is a thrombotic event.

Smoking and birth control pills lead to increased thrombotic events but I am not sure ischemic --

DR. WOLFE: Well, it seems they are at increased risk.

DR. BRANDT: Hi, my name is Larry Brandt and I was asked to come here as a consultant in ischemic colitis, which is probably the most narrow definition of my responsibilities I have ever had. So, it is a pleasure to do so.

I wanted to address the point that you made about the smoking being a risk for ischemic disease of the colon. Smoking has never been shown to be a risk for ischemic disease of the colon, although it has been shown to be a factor in the development of thrombotic disease of the mesenteric circulation. The difference between small bowel ischemia and colonic ischemia is that small bowel ischemia, in probably close to 65 percent of cases, has an anatomic abnormality that one can identify. That anatomic abnormality, be it an embolus or a thrombus, has a positive association in a very weak way with cigarette smoking. Colon ischemia has never been shown, in a majority or even a significant minority of cases, to have any anatomic factor that predisposes to it.

So, I think that although it may be a permissive factor, I don't think that there is any evidence to show

that people who smoke are at higher risk for colon ischemia than people who do not smoke.

DR. HANAUER: From your review -- take off your consultant hat and help us for a second -- do you feel that you are able to assess who is at risk for complications from this drug, given the data that you have seen?

DR. BRANDT: No, I really can't. I think that the hormone replacement therapy and the oral contraceptives are always a warning flag to me because in our younger population that is probably the most frequent associated factor, making people predisposed to develop this disease. I am not even sure that the small number of cases that were reported here show that in these cases oral contraceptives or hormone replacement therapy were particular risk factors, although in general they are.

So, my answer would have to be no, I don't. I would obviously be a little bit more concerned with people over the age of 55 than younger than 55. But aside from that very global difference, I don't see any precipitating factors.

DR. WOLFE: Larry, most of the patients you have described -- a lot of them are hospitalized patients with hypoperfusion, hypotension, surgical patients who are chronically ill. This is a different population of patients. We cannot rule out the possibility of cofactors

playing a role in etiology.

DR. HANAUER: So, the point is you would like to study potential cofactors.

DR. WOLFE: We have seen this kind of pattern with estrogens all over the place and I think, rather, the burden of proof is that it isn't a cofactor.

DR. BRANDT: I don't think anybody would disagree with doing a study to evaluate possible precipitating factors, as is planned. You were in error though when you said that the majority of my patients were hospitalized. The majority of my patients were not hospitalized if we restrict the discussion to colon ischemia, especially colon ischemia that spares the right side.

DR. HANAUER: Moving on, Dr. Welton, did you have a question regarding this? No? Dr. Kramer?

DR. KRAMER: Actually, most of what I heard this morning and what I just hearing now around the table is a question of what is the probability of having certain factors, perhaps risk factors, in people who suffer the complications. Well, it seems to me what we really want to know is what the probability of complications is in the people who have specific risk factors. That is the reverse probability of what we have just been talking about, and it seems to me the best way, and perhaps the only way, to get at that is to pursue some of the studies that were actually

planned this morning, case-controlled studies and cohort studies, analytic epidemiologic studies. I think it is far more difficult to simply look at the people who suffered complications and try to look at their risk factors and develop the reverse probability. As a matter of fact, I am not aware of a way to do that.

DR. HANAUER: Dr. Laine?

DR. LAINE: Just in terms of other risk factors again, it is somewhat intuitive but I reiterate what I said this morning, and perhaps a somewhat broader definition of recent history of constipation, thinking that those patients are alternators who shouldn't be on the drug anyway, and I would perhaps suggest, again, a slightly broader definition to include people with recent constipation within some relatively short time frame, the last couple of months or something like that.

DR. BLUM: No one yet has addressed how we are going to look at the potential for hepatotoxicity. We know that the databases do not give us that information, and I think that there is a potential. We have seen it with other drugs recently, and I think that is something that should really be addressed.

DR. HANAUER: Are you able to identify any risk factors for hepatotoxicity in the patients that you have seen?

DR. BLUM: No.

DR. WELTON: Just a follow up again on Dr. Laine's question, from the data that was presented this morning, about how many months or weeks were those episodes of constipation were that preceded these complications? Is that data available?

DR. MANGEL: No, it is not. In aggregate, no, it is not.

DR. WELTON: But for each patient, can we go back and say some patients had a history of decompaction and constipation, and is there a way to find out how far ahead that was so we could try to get a handle on what might be a relatively safe time period?

DR. MANGEL: We would be glad to go back and get as much information on that as we can.

DR. WELTON: Thank you.

DR. HANAUER: Please identify yourself for the group.

DR. MCGILL: Jim McGill, Indiana University, consultant for Glaxo regarding issues about hepatotoxicity. I would like to make just a couple of comments relevant to your comments, sir. The term has been that there are several patients -- three have been identified that have suffered hepatotoxicity. There are very few cases, and I think it bears to pay some attention to each of those, and I

think it will be evident there are fewer than that.

The two that came after release of the drug -- it is important to note the details of these patients. The first one was commented on as a 78-year old woman who came into the hospital, who was near-dead, quite frankly. She was hypotensive. Comments were made that she had ischemic limbs. She had anasarca preceding the dosing of the one dose of drug, and a week later was found to have elevations of amino transferases.

Now, I think that emphasizes nothing to do with hepatotoxicity of a drug but a very sick patient, and it would be incorrect to be thinking about that as hepatotoxicity.

The second patient is just --

DR. HANAUER: Were the other complications related to it?

[Laughter]

DR. MCGILL: No, I don't think so. I don't think any of them were.

DR. HANAUER: They took the pill and then the next day were hospitalized with all this stuff?

DR. MCGILL: I don't think it is anaphylaxis, no. In fact, the second patient was an 80-year old woman who had, I think, several weeks of drug therapy, who came in -- and it is not clear why she was hospitalized, but what is

clear is that she was hospitalized. The amino transferases were elevated, and a common bile duct dilatation was shown on a CT scan, and her amino transferases resolved very quickly.

Now, there are many things we don't know about this, but what is very compelling with the information we do have is that this patient, like many other patients, would have passed a stone and would have come, and probably because she had abdominal pain is why she was admitted, not because of some elevation of amino transferases. So, I think it would be incorrect and bad thinking and bad medicine to assert as a drug-induced complication, though it is possible but I think the evidence doesn't support that.

The first case that was presented at the time that the drug was initially approved, it is interesting to think about. That is, this patient was a younger woman who did have obesity, which is a risk factor for some amino transferase changes. She did have within four weeks, a very reasonable time course, amino transferase changes. They did persist and they normalized almost all factors within two days of cessation of the drug.

Now, the fact that in placebo and drug there were no significant differences tells us that it is unlikely that she would have had a metabolic cause for her amino transferase changes. So, then you have to be thinking that

she had some immunoallergic cause for her problems. And, she is the one who had Crohn's disease and asthma, and was taking a variety of other medicines as well.

So in that case, the one that was initially understood, it may be that she did have a drug-associated change in liver function tests but it is still hard to implicate that as a primary cause, and to say that it raises a flag of generalized hepatotoxicity because I think, although anything can happen but now, 121,000 different patients later, and there may be one person who has had some twice elevated amino transferase changes -- that is not very compelling, nor should it drive attention away from important stuff, I think.

DR. BLUM: That is only if those people had their amino transferases examined during those 120,000 people, whether physicians drew the blood or not.

DR. MCGILL: Right. Again, we know in the trials, and I have been given access to those registries, there were four patients whose course was more suspicious perhaps, that is, they are obese --

DR. HANAUER: I don't want to get into debates over these issues right now.

DR. HOUN: Yes, I think basically I am hearing that in terms of assuring patients, the issue of preexisting constipation, current constipation and a recommendation for

studies on risk factors, especially related to smoking and estrogen use, and perhaps a continued surveillance of hepatotoxicity, especially with those long-term studies the company is proposing. There is also some question about trying to exclude the alternators as well.

DR. HANAUER: I think also the issue possibly of age relationship.

DR. HOUN: Are you saying studying that as well?

DR. HANAUER: Well, the cofactor of age since most of these people did tend to be the older people who are obviously at risk in the general population anyway for those same kind of complications, but the question is whether they are at increased risk for complications.

DR. HAVLIK: Yes, make sure there are enough older persons in some of the surveillance systems that are going to be followed.

DR. WELTON: One of the things that struck me too is that there is a significant number of patients that were young that had ischemic colitis, which is essentially unheard of in the younger patients. I will defer to the expert in the audience but that really caught my eye.

DR. HANAUER: The next point that we wanted to cover is the assurance that Lotronex is prescribed to patients for whom it is indicated. I think the case reports that we have heard exemplify a number of instances where

there was a question whether or not the patients who had complications actually met the criteria for the drug -- the hepatotoxicity that we just heard about with the patient with Crohn's disease. Some of the constipation patients were alternators or had a history of constipation. So, I presume that is a component that everyone agrees with.

DR. HOUN: That is a specific goal you would recommend us to have with the company that the indicated population for the indication could be evaluated later on to see if we meet that goal?

DR. HANAUER: Again, my view is that the company or the agency isn't held responsible for people who are given drugs for unindicated reasons. That is the purpose of the indications, and clearly your job is not regulate medical practice but to assure the safety and efficacy within the confines of the population for whom it has been approved. Certainly, I think you would want to know that. You would also want to know from you follow-up studies where you do see complications if you can predict any other risk factors. Then the company will come back or practice and clinical studies will come back with whether the indication should be expanded to other populations. Yes, Dr. Kramer?

DR. KRAMER: Since we are talking about risk management in general, I am not sure how one could easily separate the concept of risk management with sensitivity and

specificity of the diagnosis. There are two things that are sobering. Presumably, you are not going to benefit people when you are treating them for an incorrect diagnosis with this medication. Secondly, it is very sobering to me --

DR. HANAUER: I don't accept that, that you are certainly not going to benefit --

DR. KRAMER: No, I said probably. You know, it is hit or miss if it has never been studied in people who don't even have the syndrome. So, it is beyond the wild guess to assume that you are going to be benefiting others, populations that have never been studied.

But, the thing of concern to me is that when you are asking physicians about their awareness of the diagnostic criteria, the prevalence of awareness was so low. That is a set-up for not only poor sensitivity in diagnosing a condition when it is there, but poor specificity in making the diagnosis when it is not there in the first place. Since the majority of the population don't have it, it is a set-up for a lot of treatment in people who don't have the syndrome. So, I would say that as part of the educational program, intertwined with risk management, there should be an effort to improve the specificity of diagnosis.

DR. HANAUER: Mr. Hammes?

MR. HAMMES: I don't think that the FDA should, at all, attempt to regulate off-label uses of drugs, and I

think that is where this is kind of heading and that is not an appropriate FDA endeavor. The education component certainly is but there are obviously going to be uses of this drug that are not in the indication and may be very rational, and we need to keep that open.

DR. HANAUER: Potentially more debatable is this next point, whether only certain physicians with special knowledge of the benefits and risks of Lotronex and of IBS should be allowed to prescribe the drug. If so, how are these physicians to be identified? Comments?

DR. WOLFE: Well, they are easily identifiable. I mean, they are gastroenterologists. That is what they are called.

DR. HANAUER: They should be gastroenterologists?

DR. WOLFE: No, I didn't say that but there are clear differences, documented recently, in prescribing practices of medication between gastroenterologists and non-gastroenterologists. For example, a drug that has been out for eleven years is prescribed by non-gastroenterologists incorrectly seventy percent of the time -- the most widely used drug in the world, as a matter of fact, and it is a real problem. Despite all the education that physicians have received, it is still being prescribed incorrectly, or let's say suboptimally -- how is that?

DR. HANAUER: So, what is your recommendation?

DR. WOLFE: Politically it is impossible to limit, I think, a drug like this to gastroenterologists only since the vast majority of patients are cared for by primary care physicians, although in an ideal world they would at least be sent to gastroenterologists for an evaluation of some sort --

DR. HANAUER: We have heard eighty percent of patients with IBS are taken care of by their primary care physician. So, only twenty percent of the doctors should be prescribing? What is the answer?

DR. WOLFE: Well, right now we have information on the drug being prescribed so far. How many are being prescribed by gastroenterologists and how many by non-gatroenterologists? How many of the complications took place with people who are non-gastroenterologists, and how many were gastroenterologists, percentage-wise?

DR. HANAUER: Dr. Laine?

DR. LAINE: I would not be in favor of restricting it just to gastroenterologists. I don't think that is reasonable. Personally, I would go more for the increased education of gastroenterologists and non-gastroenterologists.

DR. BLUM: I agree. It would disenfranchise huge numbers of people in the United States. Anyone who is more than fifty miles from a university center may not even have

access to a gastroenterologists.

DR. HANAUER: Dr. Levin, did you have comments?

MR. LEVIN: I just wondered if it would be something to track though over time, whether there is any difference in appropriate prescribing and complication rates by specialty.

DR. HANAUER: Do you guys have information on that yet?

DR. KENT: About fifty percent -- right now, remember, when we launched the drug we launched it primarily to the gastroenterology community, not to the primary care doctors initially. So, about fifty percent of the users right now are gastroenterologists. That will, of course, change over time as there is wider use and we promote it more. The complications, I am told, are about half and half gastroenterologists and non-gastroenterologists.

DR. HANAUER: Does that go the same for your advertising? Is it also only or primarily in gastroenterologic journals?

MR. HULL: Dr. Hanauer, to answer your question, we are advertising in a variety of journals but primarily, initially, in gastroenterology journals. As Dr. Kent alluded to, when we first introduced the product we called on gastroenterologists initially for the first three weeks, and then we introduced the product in a broader audience.

DR. WELTON: Just a question for the gastroenterologists, a drug like imfliximab, is that restricted to gastroenterologist use?

DR. HANAUER: No.

DR. FERRY: I just have a question, whether you know whether pediatricians are prescribing this at all? Do you have any knowledge about use under age 18, any experience?

DR. KENT: I don't think we have specific information but we would assume there is actually very little prescribing in the pediatric population.

DR. HANAUER: Did that answer your question?

DR. HOUN: I think initially the recommendation is to consider education. At a later point in your discussions we may push this issue about systems distribution again should goals not be met in terms of safety or if we see any types of adverse events or rates that you might find unacceptable, and then would this be an option.

DR. HANAUER: The next question asks about maintaining the incidence of adverse events at or below a certain level. You have given a level of about 1/1000 now for both constipation -- what would you say they are at right now?

DR. HOUN: In the trial, I think the incidence was about 1/750 for ischemic colitis, with the postapproval I

think the estimate is about 1/900 for ischemic colitis.

DR. HANAUER: About 1/1000. Dr. Brandt, what is the incidence of ischemic colitis in the general population?

DR. BRANDT: I can't answer it in the general population because I think that most cases don't come to a physician's attention. I can tell you that in my endoscopy unit we do about 3500 colonoscopies per year and we see on the order of 0-3 cases per week. So, it averages out, depending on how you round out the numbers, to between 1/450 and 1/750 colonoscopies.

DR. LAINE: We can't accept colonoscopy data, obviously. So, it is not going to be useful.

DR. BRANDT: I don't have specific data. That is the best I can do for an off-the-cuff remark.

DR. HANAUER: So back to the panel, is 1/1000 risk -- we will just take that, 1/1000 risk of ischemic event, as we have heard it, acceptable for this drug? How about the patient representative? You have heard the disease.

MR. HAMMES: I think ultimately, especially in this disease, the patient assesses their individual benefit, and it is a benefit-risk issue and the patient has to decide what a reasonable risk is. I don't know that we can set a number that 1/1000 is not acceptable, 1/1500 is. I mean, that is grabbing at straws.

DR. HANAUER: Dr. Wolfe?

DR. WOLFE: A complication of this, the severity -- I don't think we are saying the drug shouldn't be used but they have to be absolutely aware of that. This is a drug which really, as we have heard, affects a lot of people's lives in a very positive way and lets them live a normal life. They need to know ahead of time though what could happen -- risk-benefit, they need to know that in no uncertain terms.

MR. HAMMES: Well, I agree with that wholeheartedly. We need to tell them what the risks are, but then they need to decide if that risk is worth it.

DR. HANAUER: The agency is asking for a benchmark line for that.

DR. LAINE: If 1/1000 or 1/900 is causing concern now and we are developing a variety of strategies to, hopefully, manage that risk, it would seem logical to me that we would not want to accept that risk in the future; that we would want to see evidence of it decreasing somewhat, or else we wouldn't be worried about 1/900 now. So, I mean, it is hard to assess what a proper risk is for this disease. I agree, every patient has to assess it individually but I would think you just would want to see a decrease or what is the point of having -- without any education or special risk management we are at 1/1000. We should be decreasing that or we are not working.

DR. HANAUER: Dr. Levin?

MR. LEVIN: I think there are two reasons for a benchmark. One is to evaluate whether risk management interventions are being successful or not. Another is, as the drug is more widely diffused and used off-label, as it will be, are we seeing any kind of increase or spike in the incidence of toxicity? So, I think you would want to know that too. So, I think there is a dual purpose to achieving a benchmark. I don't think we should think about it as reassurance for patients because it is on such shaky ground that I don't think it is appropriate to say to patients you should be reassured that your risk is 1/1000 of an adverse event because I don't think we know that. We don't understand enough to say that with assurance to a patient. So, I really think it is for the other two purposes.

DR. WOLFE: Listening carefully to the criteria for including warnings, there are criteria involving animal studies and there are criteria involving human studies. If you look back, again, in our field, omeprazole was introduced initially with a black box warning, and that was based on studies done in rodents with clear inter-species differences, yet it was there and it was removed once it was shown that it was clearly a species-related phenomenon. I am not suggesting that is going to be the answer here, but there is precedence for it. I think the other precedence is

that if you add a black box later on, as in the case of cisepride, it is too late. People feel comfortable using the drug. So, we really have to decide how the warning is going to take place. I think we all agree that a warning of some sort is necessary.

DR. HANAUER: You are skipping ahead three points.

[Laughter]

DR. WOLFE: That is okay, we have to get out of here.

DR. RACZKOWSKI: Dr. Hanauer --

DR. HANAUER: Yes, sir.

DR. RACZKOWSKI: Most of the comments to the previous question seemed to focus on benchmarks for ischemic colitis. I wonder if people could comment what sort of toxicity levels they might accept for complications of constipation or serious complications of constipation for this drug.

DR. HANAUER: Comments? Dr. Welton?

DR. WELTON: It is good business for you, I guess -- good business for the colorectal surgeon. Actually, I just want to back up. How are we documenting the ischemic colitis? That is a real concern for me. I don't think a flexible sigmoidoscopy is going to be acceptable. It just sees internal hemorrhoids. You are going to have to go for a full colonoscopy every time to make sure the disease isn't

in the proximal half of the bowel. As far as benchmarking constipation, I am afraid I am at a loss.

DR. HANAUER: What are the committee's views on the complications that we have been presented with for constipation?

DR. LAINE: I guess the question is do we really have a denominator for the constipation complications? I don't think we do so I am not sure that we have a benchmark now. That is my problem with that.

DR. WELTON: And also the idea that it is such a personal definition.

DR. HANAUER: We are talking about serious complications. These are those requiring hospitalization, surgery, etc. That is what we are talking about. Dr. Surawicz?

DR. SURAWICZ: Yes, my concern is exactly that. I am not worried about the constipation that resolves when the drug is decreased or the doses are stopped or a drug holiday. It is these serious complications, the stercal ulcer, the perforation, the surgery. Even the last case, as confusing as it is, something happened after the drug was given and there is a temporal relationship even if not a causal relationship. So, that is what I think I would monitor. That, to me, is the alarm, the seriousness of the complications of the serious constipation. But I think the

milder constipation probably should be looked at as well to see if there are any indications in that group as to who then gets a more serious complication.

DR. WELTON: I guess my suggestion then would be anybody who requires hospitalization or even outpatient disimpaction. Anybody who requires physician intervention with disimpaction or hospitalization, in my mind, that is a serious complication of constipation for the patient and the physician.

DR. HANAUER: Dr. Lennard-Jones?

DR. LENNARD-JONES: Can I say something about these cases of constipation? One patient had had disimpaction previously. So, that is severe. Anybody who has had disimpaction before the drug is a complication with severe constipation. Another one was described as having severe idiopathic constipation, which is a very troublesome condition. So, I think we can establish that those two patients had severe constipation.

The other patients are really very complicated. The lady who had the perforation, she was in her 70s. There was no mention of constipation before the drug was given or, indeed, before surgery. I think our surgical colleague here would agree that a perforated sigmoid colon is not necessarily a complication of constipation. She might well have had a perforated diverticulum, for example.