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Glaxo Wellcome

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C O N T E N T S

P R O C E E D I N G S

Call to Order, Introduction

DR. HANAUER: I would like to call the meeting to order. We are right on time, as usual, for this event. To begin with, Tom Perez is our executive secretary and he has some meeting statements.

Meeting Statement

MR. PEREZ: Good morning. The following announcement is the issue of conflict with regard to this meeting, and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting, with the following exceptions. In accordance with 18 USC 208(b), full waivers have been granted to Dr. Michael Wolfe and Dr. George Ferry. Copies of these waiver statements may be obtained by submitting a written request to FDA's Freedom of Information Office, located in room 12-A30 of the Parklawn Building.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves

from such involvement, and their exclusion will be noted for the record.

With respect to FDA's invited guests, there is a reported interest, which we believe should be made public to allow participants to objectively evaluate his comments. Dr. Eric Holmboe would like to disclose for the record that he has been asked to teach a course on evidence-based medicine by a firm which is receiving support from Boehringer Ingleheim.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

We have an additional statement to make. Representatives of Glaxo Wellcome have asked us to bring to your attention that their briefing document was inadvertently printed and stamped "confidential." They wish to make it clear that it is a public document and completely releasable but, to fulfill the letter of the law, they have brought with them an additional set, which is the green set that is at the table. So that replaces the blue briefing document. The green replaces the blue, of similar width, just because it has "confidential" which is a very important legal consideration. Okay? Thank you.

DR. HANAUER: I was a bit remiss yesterday in not

having the panel introduce itself, and I want to fix that today. So, Dr. Talarico, could you just start and we will all introduce ourselves?

DR. TALARICO: I am Lilia Talarico. I am the Director of the Division of GI and Drug Products.

DR. HOUN: I am Florence Houn, with the Office of Drug Evaluation III, at FDA.

DR. GALLO-TORRES: I am Hugo Gallo-Torres, Medical Team Leader of the HFD-118 Division.

DR. LAINE: Loren Laine, Gastroenterology, USC Los Angeles.

DR. FERRY: I am George Ferry, pediatric gastroenterologist at Baylor College of Medicine in Houston.

DR. SURAWICZ: Christina Surawicz, University of Washington.

MR. HAMMES: Richard Hammes, pharmacist, University of Wisconsin, consumers' representative.

DR. BLUM: I am Dick Blum -- and hold on, I am an internist; I am Medical Director of United Cerebral Palsy; I also am Chairman of Pharmacy and Therapeutics at San Francis Hospital in Rosslyn, New York. I am a practicing internist and clinical pharmacologist. As the Vice Chairman of the New York State Drug Utilization Review Board, I teach clinical pharmacy at two schools of nursing and a school of pharmacy.

DR. HANAUER: We now know who is going to speak a lot!

[Laughter]

I am Steve Hanauer, from the University of Chicago.

MR. PEREZ: I am Tom Perez, executive secretary of the committee.

DR. WOLFE: I am Mike Wolfe, from Boston University.

DR. KRAMER: I am Barry Kramer, from the Office of Medical Applications of Research at the National Institutes of Health.

DR. HAVLIK: My name is Dick Havlik, and I am a physician epidemiologist with the National Institute on Aging.

DR. AVORN: I am Jerry Avorn, and I am Chief of the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital in Boston and Harvard Med. School.

MR. LEVIN: Arthur Levin, Director of the Center for Medical Consumers and Co-Chair of the FDA Consumer Consortium.

DR. WELTON: I am Mark Welton. I am a colorectal surgeon at University of California San Francisco.

DR. POWE: I am Neil Powe. I am Professor of

Medicine and Epidemiology at Johns Hopkins University.

DR. SIEGEL: Joanne Siegel. I am a consultant. My area is medical decision-making.

DR. HOLMBOE: My name is Eric Holmboe. I am a general internist, and my interest is in risk communication.

DR. GURWITZ: I am Jerry Gurwitz. I am Executive Director of the Meyers Primary Care Institute at U. Mass. Medical School.

DR. HANAUER: Thank you, and welcome, everybody. Dr. Houn, you have some opening statements, I believe.

Opening Comments

DR. HOUN: Good morning. I am very appreciative of our committee members and the members of the public for being here to help the Food and Drug Administration and Glaxo Wellcome in an important public health matter. I am also appreciative of Glaxo Wellcome for stepping forward and working with all of us to improve the risk management of Lotronex, a drug used for symptomatic relief of irritable bowel syndrome in women whose IBS is diarrhea predominant.

We have assembled quite a gathering here of intellect, wisdom and dedication to patient care and public health to help FDA embark on a new course in ensuring that the drugs that are marketed are safe and effective. Drugs play such a crucial role in health and FDA's statutory mission is to approve medical products for marketing that

are safe and effective for use under conditions prescribed, recommended or suggested in the proposed product labeling -- what we call the package insert and what many of you identify as the material printed in the PDR, the Physician's Desk Reference. Traditionally, FDA has reviewed data provided to us in drug applications for marketing by pharmaceutical companies. We have determined if an effect exists through adequate and well-controlled investigations. We have measured this effect and determined if adverse events or safety issues are present. We weigh the benefits as described by the drug's effect with the risks as described in the adverse event profile. Those drugs in which benefits appear to outweigh risk are approved, and known risks are labeled.

The labeling was seen as an end and not as a beginning of risk management. However, recently we have gotten many indications that labeling is not enough as an end-all tool and that we need more risk management planning. Physicians complain the labeling is too long. It is too complicated. It is not helpful. It is not being read. It is not being followed. We are realizing that labeling is important and it is the basis for all claims for advertising and truthful statements about the product, but maybe it is not enough for some drugs.

Thus, FDA has come to realize that safe and

effective use of drugs does not mean safe and effective theoretically as in the label, but safe and effective in the real world. FDA is concerned about how drugs are actually used; how physicians use the drugs; how the public uses them; if the medical community understands risks and benefits of the drug, and how to improve this understanding and actual safe and appropriate use of the drugs.

This problem is a complex problem that is not solved by government, not solved by FDA alone, and not solved for just one drug. Recent reports on medication errors, as documented in the Institute of Medicine's report, "To Err is Human," points to a public health crisis of mortality, morbidity and confidence. To solve some of the problems, we need to create a new culture about safe drug use. We need your help and your best advice.

We have a responsibility, along with you experts, advocates and manufacturers, to cultivate this new culture where risk management, risk intervention and evaluation is an iterative, evolving, dynamic process to promote public health. We are here today to initiate a public discussion on some very difficult issues. Some of these issues will not have one answer. For example, when we talk about adverse events, what is an acceptable society cost, business cost or individual health risk cost of a drug?

In some answers to questions about safe and

appropriate use of drugs you may not want the government involved in such activities as evaluating compliance of physicians or patients to labeling. That is fine. FDA is here to obtain your best advice, and sometimes we are part of the solution and sometimes we know we are part of the problem.

While we may be delving into large societal issues, in part we have to be grounded by this specific drug, Lotronex, and its treatment effect in the disease it is for, meaning its benefit; and this drug's specific risk profile, its known side effects, potentially attributed ones, and yet to be seen adverse events but predictable as the drug is used in a wider population in the U.S.

Some of you are thinking why are we talking abut this drug now? There are no deaths; there is only a handful of unfortunate events. Isn't the government jumping the gun? Why is FDA doing this so soon after approval, back in February of this year, when there is just a small number of events?

Well, we think it is in everyone's interest to try to assess the risk, to develop a risk management program, and to evaluate risk interventions to work for success now. While we are going to be talking about the specific drug and its benefits, we welcome you to propagate the ideas and concepts we learn today from your areas of work, advocacy,

expertise in politics, drug development, patient care. All drugs have risk and benefits. We need to work together to promote safe and appropriate use of drugs, and not only to promote this message but to make this a reality.

Thank you.

DR. HANAUER: Thank you, Florence, for that eloquent and well-spoken charge. We will do our best.

We are going to begin the presentations today with the sponsor's, Glaxo Wellcome, presentation, followed by committee discussion and then the FDA presentation before lunch. After lunch, assuming we are keeping on schedule, we would like to hear briefly from the public and then deliberate. We anticipate that we will be finished by 3:30 today. So, we would like to keep things moving and keep redundancy to a minimum. That is my charge to the committee members and the audience.

So with that, I would like to invite Richard Kent, from Glaxo Wellcome, to initiate their discussions.

Glaxo Wellcome Presentation

Introduction

DR. KENT: Dr. Hanauer, Committee members, good morning.

[Slide]

My name is Dr. Richard Kent. I am the Chief Medical Officer for Glaxo Welcome.

[Slide]

As you are aware, Lotronex is a new treatment approved for women with the diarrhea-predominant form of irritable bowel syndrome. The NDA filed for Lotronex received a therapeutic classification of priority review, the review category reserved by FDA for drugs that represent a potential significant improvement over existing therapies. The agency approved our marketing application on February 9, 2000, following a unanimous recommendation for approval at the November 16, 1999 meeting of this committee. The availability of Lotronex marked the first approval in decades of a new treatment for IBS.

[Slide]

We are here today at the request of FDA, who have asked us to present to you an overview of our risk management plan for Lotronex. We have also been asked to provide an update of the information regarding the benefits and risks of Lotronex as background for today's discussion.

[Slide]

What we intend for you to understand from our presentation is that Glaxo Wellcome is addressing issues related to risk management for Lotronex in a contemporary and comprehensive manner, focusing our effort on three primary components. The first is essential information for safe and effective use of the product. This is, of course,

accomplished through appropriate labeling. Information contained in the labeling is derived from available data at the time of approval and is updated as new information becomes available through continued research and postmarketing product surveillance.

The second component is to actively and effectively communicate new messages described in the labeling to healthcare practitioners and to patients.

The third component is a reflection of responsible stewardship on the part of a drug sponsor, that is, to take measures to determine if the message has been effectively and accurately received.

[Slide]

Our presentation today will address two fundamental issues: Has the benefit-risk profile for Lotronex changed and, if so, what are the specific data to indicate how this change is manifested? If there has been a change in benefit-risk, what action is appropriate?

In your briefing document from FDA, the agency points out that IBS is not a life-threatening condition. FDA states that Lotronex offers palliative, not curative, treatment. Further, FDA states that the benefits attributable to Lotronex occur in only a relatively small percentage of patients treated.

We believe women suffer with IBS and that this

suffering is impactful in a woman's life and is, therefore, deserving of treatment. We have fundamental disagreements with FDA on their perception of the burden that IBS represents to patients' lives, as well as the benefit that Lotronex provides to women with the diarrhea-predominant form of this disease.

To address these issues of the impact of IBS on patients' lives, Dr. Ian Gralnek, Director of UCLA Center for the Study of Digestive Health Care Quality and Outcomes, will provide an overview of the burden of disease. One of the primary frustrations of patients who suffer from irritable bowel syndrome is that, because of a lack of objective evidence of an organic source of their pain and discomfort, healthcare practitioners are often skeptical and at times trivialize the impact IBS has on their lives. Dr. Gralnek's overview is intended to appropriately frame the need for effective treatment options for IBS.

[Slide]

With regard to the safety profile, there are three major areas of focus that are identified by FDA in their briefing materials to you. Drs. Hanauer, Ferry and Laine will recall from the November 16th advisory committee meeting that these are the same areas of attention discussed during the deliberations regarding approval of the product.

The first issue is that of hepatic abnormalities.

We will present to you the data from which we conclude that there is no evidence of drug-induced hepatic injury. Accordingly, we have not proposed labeling changes in this regard, nor has FDA suggested labeling changes during our discussions with the agency.

The second safety topic that received attention during the approval process is ischemic colitis. Additional infrequent reports of ischemic colitis have been received since approval. The FDA and Glaxo Wellcome have carefully evaluated the reports from clinical trials and from our spontaneous reporting system and both conclude that the relative frequency and severity of these events are comparable to the time of approval.

The third area of interest is related to rare reports of serious sequelae of constipation that have not been observed previously. During his presentation, Dr. Mangel will describe these cases to you in some detail. We believe that this issue should be the most critical focus to ensure safe use of Lotronex.

[Slide]

In response to FDA's new initiative, Glaxo Wellcome is interested in participating in substantive dialogue regarding risk management. Today, as part of what FDA has described as a broad risk management concept discussion, we will share our plans for Lotronex. Many of

the activities that comprise our plan, such as continued research to evaluate optimized means of managing constipation, were initiated prior to approval. We have enhanced our program as new information has become available.

What we will present to you today is a plan that has resulted from significant consideration of a menu of available options. Our plan does not include every available option. This is by design. The plan has been tailored to be specific for Lotronex based on the data, and to reflect our assessment of the appropriate activities required to maximize benefit and minimize adverse effects.

[Slide]

In summary, our conclusion from review of the data is that the benefit-risk profile for Lotronex remains positive. The data we have received do not signal an emerging spectrum of serious adverse events as stated by the agency. FDA has proposed a black box warning for complications of constipation. We do not agree that a black box warning is warranted by the data. We do agree that, based on information received since the product has been marketed, appropriate labeling modifications, coupled with an appropriate communication plan, will enhance the safe and effective use of Lotronex.

Appendix 3 of the FDA's briefing document provides

the currently approved labeling for Lotronex. You have also been provided, as part of our briefing materials, with Glaxo Wellcome's proposal for modified professional labeling. We believe the proposed labeling changes and recent enhancements to our risk management plan represent responsive and appropriate action toward our goal of ensuring that adverse effects are minimized while the benefits of treatment are maximized through appropriate product use.

[Slide]

I will now introduce those who will make presentations on our behalf. Dr. Ian Gralnek, from UCLA, will present an overview of the burden of disease. Dr. Allen Mangel will then provide a review and update of the safety and efficacy data for Lotronex. Glaxo Wellcome's risk management program will be descried by Dr. Elizabeth Andrews and Mr. Stan Hull. Dr. Andrews will present an overview of the risk management plan. Mr. Hull will provide a description of the communications plan. I will then complete the Glaxo Wellcome presentation with some concluding remarks.

Thank you for your attention. I would like to turn the podium now over to Dr. Gralnek.

DR. HANAUER: Thank you, Dr. Kent. I certainly hope Dr. Gralnek will minimize the impact of the burden of

illness, as we have heard this, and focus on the benefits of Lotronex on that burden, rather than give us a general review of IBS which we have heard before yesterday and by the public yesterday -- or be brief.

IBS Burden of Illness

DR. GRALNEK: I promise you I will be brief, Dr. Hanauer.

[Slide]

Dr. Hanauer, Committee members, ladies and gentlemen, good morning. My name is Ian Gralnek, and I am an academic gastroenterologist at UCLA.

[Slide]

I am going to give you a brief overview of IBS. It will be brief. IBS is a symptom-based diagnosis with multi-symptom complaints consisting primarily of lower abdominal pain and discomfort, as well as altered bowel function which consists of sense of urgency, altered stool consistency ranging from diarrhea to very hard-formed stools, altered stool frequency, as well as a sense of incomplete evacuation. Patients will often complain also of abdominal bloating. These complaints are not explained by any identifiable type of radiographic or endoscopic findings or biochemical abnormalities.

[Slide]

Population-based studies have shown that the point

prevalence of IBS in this country ranges anywhere from 4-20 percent. This disease affects primarily females. Roughly two-thirds of IBS sufferers are women. The symptoms can cause great discomfort. These are often chronic and recurrent over a lifetime, and the symptoms can significantly disrupt daily functioning both at home or in professional life.

[Slide]

Treatment options include dietary modification, fiber supplements, as well as pharmacologic agents. The success of treatment options in addressing, however, the multiple symptoms in IBS has been limited until recently.

[Slide]

Let's talk about the prevalence of IBS diagnosis in practice. This is a disease which is not just seen by myself as a gastroenterologist, these patients are seen in a primary care setting. Upwards of 12 percent of individuals seen in primary care have a discharge diagnosis, either primary or secondary, consistent with IBS. In GI practice, approximately a third of the patients that I see or a gastroenterologist sees have a diagnosis of IBS or symptoms consistent with IBS.

[Slide]

When you are going to define the burden of a disease or burden of illness, it can often be divided into

three main areas, looking at the direct medical costs associated with the disease, or indirect costs which can be evaluated as productivity loss, as well as the personal burden of the disease which can be measured using calculated quality of life instruments.

[Slide]

Five years ago, Nick Talley and his colleagues at the Mayo Clinic published a paper that evaluated the direct medical costs associated with IBS. This was done in Olmstead County. What they found is that in their group of IBS sufferers they incurred 74 percent in more direct healthcare costs than a comparable group of non-IBS sufferers, and this was adjusted for age, gender and race between these two groups. When they extrapolated these findings to the overall U.S. population based on an 18 percent prevalence rate of IBS within Olmstead County, this resulted in upwards of eight million dollars in direct medical costs to take care of IBS patients.

In a different study, by Drossman, the U.S. Householders Survey, they found that IBS patients had more physician visits and used more resources, healthcare resources. This was not just for their GI complaints but was actually also to see non-GI physicians for non-GI complaints.

[Slide]

In that same study by Drossman, when they looked at their IBS cohort of patients compared to a control group, they evaluated the productivity burden or indirect costs. They evaluated this by looking at absenteeism from work or school during the preceding 12 months, and what they found is that the IBS patients had significantly higher rates of absenteeism from work or school. It came out to be about 13.5 days as compared to about 5 days in those preceding 12 months.

[Slide]

What about the personal burden on the patient? As I have mentioned, one way you can evaluate this is by measuring health-related quality of life, which is a multidimensional construct which attempts to evaluate the physical, psychological and social functional status as well as an individual sense of well-being.

[Slide]

Why do we want to measure health-related quality of life? Well, it can help define the burden of disease. In addition, traditional physiologic endpoints which we often study do not always equal an individual's functional status or their self-reported functional status or well-being. An example may be two individuals with chronic obstructive pulmonary disease who have identical pulmonary function tests yet, if you were to measure their health-

related quality of life, they may give you different results. In addition, health-related quality of life outcomes matter to the patients. This is the patient's voice.

[Slide]

These are data which were published three years ago by Wells using the SF-36. The SF-36 is a generic health-related quality of life measure. Scores range from 0-100, with higher scores meaning better health-related quality of life. The SF-36 captures 8 different domains. It evaluates an individual's physical functioning, physical role limitations, bodily pain, general health perceptions, vitality, individual social functioning, emotional role limitations and mental health.

When they compared their IBS cohort to U.S. normative population data on the SF-36, they found that across all eight scales the IBS patients reported significantly worse health-related quality of life.

[Slide]

These investigators went on and compared their IBS cohort to historical data on type II diabetics as well as patients with clinical depression. These data on these two cohorts came from the medical outcome study. The medical outcome study was a four-year observational study of the processes and the outcomes of care in different practice

settings in this country, looking at different chronic conditions which included diabetes as well as depression. What they found is that when you compare the IBS patients to the diabetics, physical functioning was similar between the groups, however, on the remaining seven scales the IBS cohort reported significantly worse health-related quality of life as compared to these diabetics.

I will also tell you that 44 percent of this group of diabetics in the medical outcome study had some type of a complication from their diabetes, whether it be retinopathy, neuropathy or nephropathy.

[Slide]

When you compare this IBS cohort to the clinically depressed patients, they were similar across 6/8 scales. However, the IBS patients has significantly better mental health functioning according to the SF-36 self-reported scores.

[Slide]

Whitehead also compared to medical study outcome data. They had a separate IBS cohort which they compared. One of the tracer conditions in the medical outcome study was congestive heart failure. The IBS patients on physical functioning had significantly better health-related quality of life. However, on the remaining scales these two disease states were comparable.

[Slide]

Now, we just finished a study which will be published in Gastroenterology this fall. The aim of that study was to compare the impact of IBS on patients' health-related quality of life, again, to previously observed general population data using the SF-36 as well as in selected chronic diseases. We evaluated almost 900 adult IBS patients who were seen at UCLA. These patients met Rome criteria or Manning criteria for IBS.

[Slide]

We compared their SF-36 data to the general population and with a group of moderate to severe patients with gastroesophageal reflux disease, patients with dialysis-dependent end-stage renal disease, and again that same group of historical patients from the medical outcome study. We adjusted for age and gender, and we adjusted for multiple comparisons between groups.

[Slide]

The data looks very similar. When we compared again to this cohort of the U.S. population, the normative data of the SF-36, our IBS patients, our cohort, scored significantly worse on all eight scales of the SF-36.

[Slide]

As compared to the moderately to the severely affected GERD population, scores were almost identical on

physical functioning between these two groups, however, on the remaining seven scales of the SF-36 the IBS patients scored significantly worse than the GERD patients.

[Slide]

What about compared to the diabetics? This is again that group from the medical outcome study. The IBS cohort scored worse in the domains of physical role limitations, bodily pain, their vitality, their social functioning, their emotional role limitations and their self-reported mental health, and they actually reported comparable general health perceptions to those of the diabetes group.

When comparing the IBS group to the end-stage renal disease patients, the IBS group had worse mental health and had comparable self-reported bodily pain, vitality, social functioning and emotional role limitations as those of the dialysis-dependent end-stage renal disease patients.

Lastly, when we compared to the depression group, the IBS patients had worse bodily pain, yet reported significantly better vitality, emotional role limitations and mental health.

[Slide]

These are physical component summary scores from our study. This is a way of boiling down the eight scale

scores of the SF-36 into a physical component summary score and a mental component summary score. Again, what we show here is that the IBS cohort scored significantly worse on their physical component summary score as compared to the U.S. general population normative data. GERD and depression samples had comparable physical component summary scores as those of the diabetes patients from the medical outcome study, and were significantly better than the renal disease.

[Slide]

On the mental component scores the IBS patients scored significantly worse as compared to these comparison diseases in the U.S. normative population data. It was significantly better in terms of mental component summary scores as to the clinically depressed group.

[Slide]

Let me summarize. There is significant disease burden in IBS. I can tell you from the patients that I see that this is not a trivial disease to them when they are being affected and they are coming to see you. It can lead to increased direct medical costs. It can lead to increased absenteeism from work or school, which are indirect costs that are difficult to measure. Lastly, there are several studies now in the literature, and ours will be coming out this fall, which show that there is a significant impact on an individual's health-related quality of life due to their

underlying irritable bowel syndrome.

Thank you all very much. I will now turn the podium over to Dr. Allen Mangel.

DR. HANAUER: Thank you, and Allen, we look forward to your presentation on how Lotronex has impacted on healthcare costs, absenteeism and productivity and health-related quality of life.

Safety and Efficacy

DR. MANGEL: I see, Dr. Hanauer, that we will have an interesting question session afterwards.

[Slide]

Dr. Hanauer, members of the advisory committee, ladies and gentlemen, good morning. I will discuss the safety and efficacy of alosetron, both around the time of approval and give you an update.

[Slide]

Alosetron is a potent and selective 5HT3 receptor antagonist. 5HT3 receptors have been shown to participate in both motor and sensory processes within the gut, thus constituting a rational basis for the proven efficacy of alosetron.

[Slide]

At the time of approval we had conducted two pivotal phase III studies. Each of these enrolled over 600 patients and they were conducted exclusively within the

United States. Only female patients were enrolled into the study based upon the results of our phase II program, and both diarrhea-predominant IBS patients as well as those with an alternating bowel pattern were enrolled. Patients were enrolled into a 2-week screening period, followed by 12 weeks of treatment with either placebo or 1 mg alosetron, each given on a b.i.d. dosing. Following completion of the treatment phase, there was a 4-week follow-up period with no treatment.

[Slide]

The primary endpoint in our phase III program was adequate relief of IBS pain and discomfort. The primary instrument or measure for the adequate relief endpoint was the following question: "In the past seven days have you had adequate relief of your irritable bowel syndrome pain and discomfort?" To this question, patients would answer either a "yes" or a "no."

[Slide]

Shown on this slide are the results from the two pivotal phase III studies. The 3001 study is shown on your left, the 3002 study on your right. On the Y axes you see the percent of individuals answering the adequate relief question as a "yes" and on the X axes are the individual weeks of the study.

As you can see, in the 3001 study significant

improvement occurred with alosetron, as represented by the yellow line, by the end of the fourth week of treatment. Significant improvement persisted throughout the remainder of the treatment phase. When you stopped treatment with alosetron symptoms rapidly returned.

A very similar pattern was also noted in the 3002 study, with the exception of an earlier onset of activity in this study. Significant improvement was noted by the end of the first week of treatment. Significant improvement persisted throughout the remained of the treatment phase. When you stopped treatment symptoms returned.

We view these data as showing strong independent replication, as well as a high degree of efficacy within this patient population.

[Slide]

As was mentioned by Dr. Gralnek, IBS is a multidimensional disorder and alosetron produces multidimensional improvement. Shown on this slide are the effects of alosetron on urgency. As we know, urgency is the unpleasant sensation that individuals need to rush to the bathroom. Thus, a reduction in days with urgency is of therapeutic benefit. In each of the studies significant improvement in urgency occurred by the end of the first week of treatment. Benefit was noted throughout the treatment phase. When alosetron was stopped symptoms resumed.

[Slide]

When we evaluated effects of alosetron on stool frequency, a very similar pattern was also noted with significant improvement after the first week of treatment; significant improvement throughout the treatment period. When alosetron is stopped symptoms resume.

[Slide]

Finally, on stool consistency, once again, there was a virtually identical pattern. These results, of course, are presented for the diarrhea-predominant population, which is the labeled population for Lotronex.

[Slide]

I would now like to update you on the efficacy of alosetron post-approval.

[Slide]

We have conducted two large international comparative studies. Each of these studies had over 600 female patients enrolled. The study design was virtually identical to that of the placebo-controlled study. Alosetron was compared to mebeverine and trimebutine, the two most commonly used agents, for the treatment of irritable bowel syndrome, in Europe.

[Slide]

Weekly adequate relief or the adequate relief endpoint once again was the key endpoint in this study. As

you can see, looking at the weekly adequate relief graphs -- this is mebeverine and this is trimebutine -- alosetron is superior to either of the comparator agents.

[Slide]

We have also recently completed study S3B30011, which is a study which enrolled 783 female diarrhea-predominant IBS patients to 12 weeks of treatment with either alosetron or placebo. In this study a global improvement endpoint was evaluated.

[Slide]

The specific global improvement instrument or question was the following: "Compared to the way you usually felt during the 3 months before you entered the study, are your IBS symptoms over the past 4 weeks" -- and patients could answer between substantially worse or substantially improved. A global improvement responder was prospectively defined as individuals who had either reported moderate improvement or substantial improvement.

[Slide]

Evaluation of the results of this study show both significant and substantial efficacy with alosetron as compared to placebo. At each monthly interval, significant benefit is noted over placebo. The magnitude of this benefit is on the order of 30-35 percent.

[Slide]

Our overall efficacy conclusions are that, as noted by Dr. Gralnek, IBS is a multidimensional disease. In diarrhea-predominant female patients alosetron produces robust improvement on multiple endpoints.

[Slide]

I would like now to turn our attention to review of the safety data base, once again, around the time of approval and where we are now. As outlined by Dr. Kent, there will be three areas of discussion in particular today, constipation, ischemic colitis and hepatic function.

[Slide]

In anticipation of today's meeting, Glaxo Wellcome and the FDA has had numerous teleconferences as well as face-to-face meetings as the intent was to have the primary focus of the meeting be on the risk management plan. We agree that there has been no change in the frequency and/or severity of ischemic colitis since the time of approval of alosetron. Glaxo Wellcome and the FDA reconciled the number of cases of ischemic colitis as well as serious cases of constipation.

At the November 16th, 1999 advisory committee meeting, Glaxo Wellcome presented alternative etiologies for some of the cases of ischemic colitis. Once again, because the FDA requested that the focus of today's meeting be on risk management rather than a review of pathology, at the

request of the FDA Glaxo Wellcome agreed that pathology of ischemic colitis will not be discussed today.

[Slide]

We have two sources to gather or analyze safety information now that alosetron is marketed. The agreed cut-off date for information with the FDA was June 1, 2000. At the time of approval of alosetron, there were approximately 3000 subjects exposed to alosetron in the clinical development program. In the clinical development program as of June 1, there have been 6852 subjects exposed to alosetron. As of the June 1 cut-off date, there were 130,000 prescriptions for alosetron which had been dispensed.

[Slide]

The first event which I would like to discuss is constipation. As we all know, many drugs have the potential to induce constipation, and there are several recognized complications of constipation, including impaction, obstruction, ileus, megacolon and perforation.

[Slide]

In the alosetron phase II and phase III program at the time of approval, constipation was our most frequent adverse event, 27 percent of patients treated with 1 mg b.i.d. alosetron had reports of constipation while 5 percent of placebo-treated patients did. Of the patients who became

constipated in the phase II and III program, 65 percent of the patients reported constipation as either mild or moderate in severity; 75 percent of the constipated patients reported only 1 episode of constipation during the course of the phase II and III program, and the median duration of the constipation was on the order of 6 days and the median time to onset was 10 days.

Because we viewed bowel function as important and relevant endpoints in an irritable bowel syndrome study, laxative use was prohibited in the phase II and phase III program. Although laxative use was prohibited, only 10 percent of patients in phase II and phase III withdrew secondary to constipation.

[Slide]

In the phase III program if individuals went 4 consecutive days without a bowel movement, then a brief interruption of alosetron therapy was mandatory. During the course of the phase III program 9 percent of patients reported 4 consecutive days without a bowel movement. Very importantly, during this 4-day interruption 88 percent of the patients undergoing the interruption resumed bowel movements in the window, and remained in the study and, of course, resumed on treatment.

[Slide]

At the time of approval, there were no serious

adverse events related to constipation reported. As of the June 1 cut-off date, there were 2 events reported in the clinical development program and 4 events in the spontaneous database. As mentioned by Dr. Houn, there have been no deaths attributable to alosetron.

[Slide]

I would like to very briefly review each of these cases, and a more detailed narrative is presented in your briefing document. Starting with the two cases which have developed in the clinical development program subsequent to the time of approval, the first individual is a 54-year old female who, following 7 days of treatment with alosetron, developed constipation and pain. She was hospitalized for disimpaction. This patient reports that she previously had a history of constipation, as well as having previously been hospitalized for disimpaction prior to initiation of alosetron therapy.

The second case is a much more complicated case. It is a 56-year old female. Prior to enrolment into the clinical trial a colonoscopy was required. Colonoscopy was attempted and terminated at 40 cm due to large volume solid stool. Clearly, the patient was constipated. The patient was re-prepped and then a colonoscopy was eventually successfully performed. Following 27 days of treatment with alosetron, she developed pain, emesis and constipation. She

went to the emergency room and was admitted to rule out small bowel obstruction versus an ileus. The patient's clinical status deteriorated somewhat as she went to surgery. At the time of surgery she was noted to have dense abdominal adhesions from the omentum to the interior abdominal wall. The transverse colon was also noted to be markedly or densely adhesed, massively dilated, along with the right and left colon. At the time of surgery there was also the note of patchy areas of necrosis, although there was no obvious perforation of the bowel. The individual had a colectomy, had a complicated hospital course, recovered and was discharged to home. The proposed sequence of events by the physicians caring for her at her local setting was that the patient developed an obstruction due to stool, megacolon with secondary ischemia.

Clearly, in each of these two cases where a complication related to constipation had occurred the individual had a prior history of constipation.

[Slide]

I will now review the 4 cases in the postmarketing spontaneous database. The first individual is a 48-year old female. Following 7 days of treatment with alosetron, she developed constipation resulting in obstruction. She was hospitalized. A colonoscopy was done and an ulcer was noted in her transverse colon. This patient has a history of

idiopathic constipation.

The next case was a 50-year old female. Following 21 days of treatment with alosetron, she reported to her physician that she had no bowel movements for 4 days. The patient was admitted for impaction and obstruction. She received supportive care and was discharged to home within 23 hours.

The next case is a 68-year old female who developed constipation after 2 days treatment with alosetron. Alosetron was stopped. Two days later the patient went to her physician with complaints of abdominal tenderness, distention and constipation. A CT scan was performed which suggested diverticulitis, and she was hospitalized with the diagnosis of rule-out diverticulitis. Two days later she was discharged to home in good condition on clear liquids. Two weeks later she returns to her physician with similar complaints and is once again readmitted with a diagnosis of rule-out diverticulitis.

Please keep in mind that this individual received alosetron for 2 days worth of therapy. She is now being readmitted 18 days after completion of her 2-day course. With that admission, an x-ray revealed old contrast in her colon from the previous CT scan. A temporary loop colostomy was performed. She was decompressed and discharged to home in good condition. A follow-up colonoscopy, performed

approximately a month later, revealed non-specific colitis in her sigmoid colon as well as an 8 mm in diameter sigmoid stricture.

The last case is a 72-year old female who reported using hydrocodone several times per week. This patient is also reported to have alternating constipation-diarrhea IBS, and 17 days after initiating alosetron therapy she developed pelvic pain, went to the emergency room and a CT scan noted a mass outside her sigmoid colon. She went to surgery, was noted to have a sigmoid perforation with an abscess. She was treated with antibiotics and after two weeks was discharged to home. In this person's history there is no mention of constipation either prior or during treatment with alosetron.

[Slide]

Our overall conclusions with respect to constipation are that constipation is the most frequent adverse event noted with alosetron. There have been rare reports of complications of constipation since the time of approval of alosetron. In 3/6 individuals in whom there have been complications, this individuals had preexisting history of constipation and, clearly, the drug was given inappropriately to them. There have been no deaths, once again, associated with alosetron and constipation.

[Slide]

The next area which I would like to review is that of ischemic colitis.

[Slide]

At the time of approval, there were 4 reports of ischemic colitis in the alosetron clinical development program. There were approximately 3000 subjects exposed to alosetron at that point of time, yielding a rate of about 1 case out of 750 exposures. As of the June 1 cut-off date, there were 3 new reports in the clinical development program, yielding a total of 7 reports out of 6852 subjects exposed, a rate of approximately 1/980. Each of these cases represented acute transient ischemic colitis without sequelae and without a grade change in severity since time of approval. Once again, there were no deaths.

[Slide]

In our spontaneous database as of June 1, 2000, in which there have been 130,000 prescriptions dispensed, there were 5 spontaneous reports of ischemic colitis. All represented acute, transient and self-limiting disease. There were, once again, no sequelae and no deaths.

The FDA contacted us yesterday and asked if we would also review a case which came in after the cut-off. So, of course, that information is not included in your briefing document and so I will walk through the narrative. It is somewhat of a complicated case in terms of following

the timing of various events. So, I have a time line up here which may just help in following the case.

The patient is a 69-year old female. On March 16, she initiated alosetron therapy for treatment of her IBS. While on vacation, on March 22 she noted cramping abdominal pain, vomiting, fever and elevated white count. She was admitted to the hospital. At that point of time alosetron therapy was stopped. A CT scan at that point in time noted thickening and thumb-printing of her transverse colon distal to the hepatic flexure and ending proximal to the splenic flexure. A colonoscopy and biopsy was performed. We don't actually have the reports on either, however, they are reported as being consistent with the development of ischemic colitis. On March 27, the patient was discharged to home in good condition.

Approximately 3 weeks later, the patient returned to her physician, complaining that her usual diarrhea has now once again returned. At that juncture, the physician also noted a maculopapular rash on her abdomen and ulcers on her right hip. The physician began prednisone therapy with a presumptive diagnosis of inflammatory bowel disease. One week later she returns to the physician, doing well with respect to her diarrhea on prednisone. A new ulceration was noted on her lip. Approximately 10 weeks after stopping her 5-day course of alosetron, in other words on Jun 4, the

local physician is made aware that she is hospitalized for a bowel obstruction. The CT scan reveals a dilated ascending and transverse colon, with a stenosis in her mid-transverse colon.

Exploratory laparotomy is performed and the patient has resection of her transverse colon. At the time of surgery, it is noted that she has multiple old sutures in her colon wall. A circumferential area of ulceration in the colon is noted in the transverse colon. There were sutures within the wall of the ulcer and a 1.5 cm sutured surgical defect. The area of stenosis was the area of the previous surgical repair. Thus, in essence, this patient has a history of a colonic process prior to initiation of alosetron therapy; has a history of a colonic process once again requiring surgery 10 weeks following discontinuation of alosetron.

[Slide]

In an effort to try and determine the frequency of ischemic colitis in populations similar to those in the clinical trials, we have begun contacting large practices and simply inquiring about the rates or number of cases of ischemic colitis. Three large GI practices were contacted and data was obtained from the practices between May of '95 and May of 2000. These practices saw 110,000 patients and 188 cases of ischemic colitis were noted or, in other words,

approximately 1 case per month per practice.

The Duke University database -- information was also obtained between July of '93 and November of '99. During that period of time there were 14,478 colonoscopies and 130 cases of ischemic colitis.

[Slide]

Our overall conclusion is that ischemic colitis appears more frequently than at least was recognized by us. Dr. Lawrence Brandt, a world-recognized expert on ischemic colitis, is with us here today and I am sure during the answer and question session, if the advisory committee is interested, he would be glad to share his experience on the frequency.

Our overall conclusions with respect to ischemic colitis are that there has been no change in frequency and/or severity of ischemic colitis since the time of approval. All cases of ischemic colitis represent acute transient ischemic colitis without sequelae. Clearly, at least in our estimation, this last case that was presented represents a patient with a colonic process prior to initiation of alosetron therapy in which she needed surgical intervention of her transverse colon. The patient had an event while on alosetron therapy, and 10 weeks after completing her 5-day course of alosetron once again required surgical intervention in the same region that required

previous surgical intervention, as well as the suspect region of her event while on alosetron.

[Slide]

I would now like to very briefly review our hepatic database.

[Slide]

We scrutinized liver function testing during the course of our clinical trial. In particular, we evaluated elevations in ALT greater than 3-fold normal at the time around approval. We had 0.4 percent of the patients treated with placebo, showing ALT elevations greater than 3 times normal and 0.5 percent on alosetron-treated patients. For the studies which have completed subsequent to approval, 0.9 percent of placebo-treated patients show elevations of ALT greater than 3 times normal, and 0.4 percent of alosetron-treated subjects. In aggregate, our database shows identical elevations of ALT greater than 3-fold normal in both placebo- and alosetron-treated subjects.

[Slide]

We also evaluated our patients' alkaline phosphatase and bilirubin greater than 2-fold normal and, as you can see on this slide, elevations in those two parameters are noted. Very importantly, no alosetron-treated subject was noted to have ALT elevations greater than 3-fold normal and bilirubin elevations greater than 2-

fold normal.

[Slide]

In the current alosetron label one patient with hepatitis without jaundice is noted. Included in your briefing document are two additional narratives from the 130,000 prescriptions dispensed for alosetron of individuals with elevations in liver function tests. One case clearly represents a case with multiple confounding factors, including heart failure beginning 3 weeks prior to alosetron initiation, as well as a history of multiple drug allergies. Dr. James McGill, a hepatologist from Indiana University, is here with us today in case the advisory committee also would like expert hepatology opinion.

[Slide]

Our overall conclusions on hepatic functions are that we believe there is no signal for hepatic toxicity with alosetron. The rates of ALTs are similar on alosetron as seen on placebo.

[Slide]

In this postmarketing spontaneous database there have been a total of 201 serious reports. You have seen 11 of these today or within your briefing document. There were the 5 cases of ischemic colitis, 4 cases of constipation and the 2 cases of elevated liver function tests. The additional 10 reports are illustrated here. Two people were

hospitalized with abdominal pain. Two individuals were hospitalized with overdoses of other medications but who happened to be taking alosetron. There are also single reports of these various events.

[Slide]

Our overall conclusions on the safety and efficacy are that IBS is a significant disease with a large burden of illness for the individual patient. Alosetron produces robust, multidimensional improvement in the treatment of female diarrhea-predominant IBS patients.

[Slide]

No change in the frequency and/or severity of ischemic colitis is noted since the time of approval. There have been rare complications of constipation. Overall, we believe the risk-benefit ratio shows a clear benefit of alosetron.

We will be glad to discuss quality of life data during the question and answer session, and I now would like to turn the podium over to Dr. Elizabeth Andrews, who will begin our presentation on risk management.

Risk Management

DR. ANDREWS: Good morning, Dr. Hanauer, members of the committee, ladies and gentlemen.

[Slide]

I am Elizabeth Andrews, and I direct the worldwide

program of epidemiologic research at Glaxo Wellcome. I am pleased to describe for you today an overview of our risk management program and some of its key elements.

[Slide]

We have developed a program that demonstrates our commitment to responsible product stewardship. This commitment includes three components: the scientific foundation for defining risks and predictors of serious events; effective communication to educate healthcare practitioners, pharmacists and patients; and program evaluation to help determine if and when our efforts need revision. The overall program is aimed at optimizing the benefit-risk profile of Lotronex.

Our company is committed to working with the Food and Drug Administration to develop a program tailored to the unique characteristics of Lotronex and the needs of women who suffer with IBS. This program builds on our experience with other drugs in which we have utilized epidemiologic and clinical research methods to evaluate drug safety both in advance of and in response to safety signals.

[Slide]

Our risk management program represents a multidimensional, integrated approach. The first dimension is risk definition, an extensive program of epidemiologic, clinical and mechanistic studies to evaluate and quantify

risks and explore risk factors for adverse events.

[Slide]

The second dimension of risk management includes a strong communications program targeted to physicians, pharmacists and patients. Our program will deliver three key safety messages around appropriate use: patient selection, management of constipation, and early detection of the symptoms of possible ischemic colitis. Of special note is a unique and dedicated program, an appropriate use program, that Mr. Hull will describe in a few minutes.

[Slide]

The third dimension of risk management is program evaluation. This dimension includes testing of the communication material for understanding, in the target population, an awareness tracking program to assure our messages are being heard, and monitoring of actual prescribing through a health maintenance organization database.

[Slide]

Of course, the key to monitoring risk management is the continued vigilance of safety through epidemiology studies and enhanced spontaneous reporting.

[Slide]

This represents a multidimensional, integrated program in risk management across all components of the

program. We will have our first systematic evaluation this December. Quarterly reviews of available information are planned by an internal team that crosses many functions within our company.

[Slide]

It is important to mention that we are in an excellent position to guide appropriate use. Lotronex has only recently been launched, and interest in IBS and in IBS treatments is high. We have an integrated plan consistent with the safety profile of Lotronex. In developing our plan, we have consulted with numerous experts in the fields of gastroenterology, epidemiology, risk management and patient adherence. We have engaged in discussions with members of the network of CERTS, the Centers for Excellence in Research and Therapeutics.

We have conducted an extensive review or our scientific data, the current benefit-risk profile of Lotronex and the options available for inclusion in a risk management program. We have proposed those activities that address the specific issues of Lotronex safety. The main clinical issue is constipation. The best way to avoid complications of constipation is by appropriate patient selection. Patients who are constipated should not start Lotronex.

The two important adverse events we are discussing

today, constipation and ischemic colitis, are recognizable by early symptoms. Appropriate action can be taken to avoid sequelae. Our program is, therefore, tailored directly to communicating the straightforward ways of reducing the risks and increasing the benefits of Lotronex.

[Slide]

Next, I would like to describe the epidemiology program of research. Epidemiology studies can provide information that simply cannot be obtained from clinical trials. A key benefit is the large numbers of patients that can be studied. The setting represents the real world in which patients are more heterogeneous than in clinical trials, and compliance and patient management are clinically dictated, not protocol driven. These studies can evaluate infrequent and rare events and evaluate risk factors that might not have been included in clinical trials. Here we trade the depth of data collected in clinical trials for breadth of study possible at the population level.

[Slide]

A series of studies has been designed to address three basic questions: What is the frequency of complications of constipation in Lotronex users in actual clinical practice? What is the frequency of ischemic colitis in Lotronex users compared with other populations, persons with IBS, persons who consult GI specialists, and

the general population? And, what are the important risk factors for these outcomes that might guide treatment and management practices?

[Slide]

In this program we will use an observational cohort design to evaluate the incidence of clinical outcomes and nested case control studies to evaluate risk factors. Case control studies afford great efficiency of design and allow use of a smaller number of patients about whom in-depth data can be obtained.

In some of our studies we will make use of large existing databases, such as health maintenance organization databases, which can be supplemented through abstraction of medical records.

[Slide]

Evaluation of ischemic colitis presents some methodologic challenges. These challenges include possible misdiagnosis as other conditions, such as inflammatory bowel disease, and the spectrum of disease that ranges from acute transient disease, similar to the cases we have observed, to more serious disease with sequelae.

Another challenge is the non-specificity of the ICD-9 coding system. These challenges will be addressed by casting a wide net of diagnostic codes to identify possible cases and then obtaining supplemental information to confirm

actual diagnosis. Such methods have been successfully used to evaluate other events that have no clear or unique diagnostic codes.

[Slide]

I would like to now describe our large observational cohort study. This will be a study in 10,000 patients receiving Lotronex. We have discussed this study with the Food and Drug Administration and reached agreement on the general design at the time of Lotronex approval. The original focus was on ischemic colitis. We are now modifying the design to include complications of constipation.

[Slide]

The objectives of this study are to define the incidence of and risk factors for complications of constipation in patients receiving Lotronex; to define the incidence of and risk factors for ischemic colitis in patients taking Lotronex; and to describe the incidence of these two events in the general population and in IBS populations not receiving Lotronex. The comparisons will include the time period prior to Lotronex introduction as well as the period contemporary with Lotronex use.

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This study will be conducted within the research database of United Health Care in collaboration with the

Epidemiology Research Institute. United Health Care is the second largest healthcare company in the United States. The research database is a subset of the entire database and includes seven million members with coverage since 1990, and who have both medical and prescription drug coverage.

This study will be conducted in three phases. In the first phase we will develop and refine the methodology, including the development of algorithms for using ICD-9 codes to identify individuals with IBS and those with ischemic colitis. In phase two we will evaluate the incidence of our clinical outcomes among Lotronex users. In phase three we will compare the rates of our clinical outcomes between Lotronex users and the two comparisons groups -- persons with IBS and the general population.

[Slide]

Also within this United Health Care study will be a utilization study, a study of Lotronex prescribing patterns. We will periodically monitor utilization to characterize the patient population by age, gender and medical and claims history suggestive of constipation. We will, further, characterize these patients based on IBS physician visits and medications.

[Slide]

Utilization patterns may provide information to suggest opportunities for enhancing our communications

effort. It is, therefore, also a part of the program evaluation component of our risk management plan. We considered long and hard how best to define a target goal of appropriate prescribing. We sought consultation with a variety of experts and we considered different approaches. In the end, we came to understand that there is no established benchmark for this measure in general, and no target level of change in prescribing that could reasonably be established a priori. Moreover, it is too early in the marketing experience to describe the current prescribing patterns due to time lags in obtaining both clinical and prescription data.

Our considered view is that we must evaluate prescribing critically and over time to evaluate patterns and look for signals that would suggest directions for further follow up in our communications program. Our first systematic review will be conducted in December of this year, and will be repeated quarterly thereafter.

The next two slides summarize all five of our epidemiology studies. I have already described the safety study on 10,000 Lotronex users. Initial data will be available in December from this study, and we estimate it may require up to two years to accrue the full cohort.

Our other studies attempt to better understand background rates of complications of constipation and

ischemic colitis. We are already conducting extensive analyses using the general practice research database, the GPRD, to estimate the incidence of both outcomes.

We plan a nested case control study to explore the contribution of risk factors, in collaboration with the Boston collaborative drug surveillance program. The GPRD is a database that consists of electronic medical records of over six million individuals in the U.K., dating back to 1989. This database represents one of the richest sources of information in existence on medication use and clinical history. These studies should be completed by the end of this year.

[Slide]

We are also initiating two similar studies that will describe the incidence of ischemic colitis and explore risk factors to help fill in the gap in our general scientific knowledge about this outcome. One study will use records from Tennessee Medicaid through collaboration with Vanderbilt University. The Medicaid population includes 1.4 million individuals, a large majority of whom are women.

The second study will be conducted by investigators at the Mayo Clinical based on the Rochester Epidemiology Project. This project has for decades followed the clinical history of all residents of Olmstead County, Minnesota. Both of these studies will be completed within

two years.

We are currently refining a protocol for a case control study that will be based on our existing and ongoing clinical trials to characterize cases of ischemic colitis and a sample of non-cases within Lotronex users to better understand risk factors, including possible genetic risk factors. The number of events is small, but we do not want to miss the opportunity to evaluate this experience systematically and in depth. This study is planned to begin this summer.

To summarize the epidemiology program of research, we have a safety study in 10,000 patients receiving Lotronex; 4 additional studies to evaluate background frequency of events of interest; and an ongoing study of utilization patterns.

[Slide]

Our risk definition program also includes a program of clinical studies. As Dr. Kent mentioned, we are committed to conducting a clinical trial that will provide additional evidence to better guide health practitioners and patients in managing constipation when it occurs on Lotronex. This study will be a randomized, double-blind, placebo-controlled study to evaluate three methods of constipation management -- laxative use, therapy interruption and dose reduction. The protocol for this

study is currently under discussion between Glaxo Wellcome and the Food and Drug Administration.

One of the most powerful ways to evaluate safety is through experience in diverse populations and different underlying conditions. Through our ongoing clinical program, additional indications and populations are being evaluated. This experience provides an expanded opportunity for safety monitoring with in-depth analysis of adverse events.

[Slide]

Another important component of our risk definition plan is a program of mechanistic studies. These studies attempt to understand mechanisms, if any, that may relate to a link between Lotronex and ischemic colitis. The first study is an in vitro test that will assess the effect of Lotronex on cultural endothelial cell integrity. This study will be initiated very shortly.

The second study will assess mesenteric blood flow in humans before and during Lotronex administration by using positron emission tomographic scanning techniques. This study will be conducted by Dr. Allan Fishman, at the Massachusetts General Hospital, and the protocol for this study is currently under development.

The third study is an open-label study that will evaluate the effect of Lotronex on coagulation parameters.

In addition, the effects on coagulation factors of co-administration of Lotronex and an oral contraceptive will be determined. This study should also begin very soon.

[Slide]

The risk definition program, as you have seen, is an extensive program designed to address the specific issues related to the benefit-risk profile of Lotronex. Our total experience, represented by the studies I have described and the clinical trial experience, will include approximately 20,000 to 25,000 patients exposed to Lotronex and monitored carefully for safety.

We have a plan in place for the evaluation of the scientific evidence on an ongoing basis. In advance of these data, however, we also have communications planned to assure appropriate use of Lotronex to minimize risks to women who suffer from IBS and who might consider treatment with Lotronex. This communications program will now be discussed by Mr. Hull. Thank you.

Risk Management Program Communications Plan

[Slide]

MR. HULL: Dr. Hanauer, members of the advisory committee, invited guests and representatives of the Food and Drug Administration, my name is Stan Hull and I am the Vice President and General Manager of the CNS and Gastrointestinal Division at Glaxo Wellcome. I am

responsible for the commercial functions of marketing and sales, and Lotronex is one of the products in my areas of responsibility.

[Slide]

As Dr. Andrews highlighted previously, our risk management program is a multi-faceted and integrated approach, and I am here to introduce the communications and evaluation components of the program, and to demonstrate the corporate commitment of Glaxo Wellcome to this program.

[Slide]

We have very specific objectives for our program, and those are the identification of patients who are appropriate candidates for therapy with Lotronex, and those patients are women with IBS whose predominant bowel symptom is diarrhea. We will also communicate which patients are not appropriate candidates for therapy with Lotronex. We will communicate important information on the potential for constipation and information as to the proper management of constipation if it occurs. Lastly, we will communicate information that helps healthcare practitioners and patients recognize the early signs and symptoms of ischemic colitis and the recommended actions to take.

[Slide]

These are the audiences to whom we will direct the elements of our communications program. We will direct

specific communication elements to healthcare practitioners and their office staff. In addition to physicians, we will also include family nurse practitioners as well as physicians' assistants in these efforts. We also have specific communication vehicles directed to hospital and retail pharmacists, and equally important, we have proposed specific information to patients who receive prescriptions for Lotronex.

[Slide]

This slide highlights the key elements of our communications programs: a "dear healthcare practitioner" letter that I will discuss in greater detail; the appropriate use program to which Dr. Andrews referred previously; revised print and website materials; additionally updated speaker educational programs; and supplemental training of the Glaxo Wellcome sales representatives.

[Slide]

Dr. Kent discussed earlier that Glaxo Wellcome has proposed revisions to the current prescribing information for Lotronex. We are confident that these revisions are an important first step in accomplishing our communications objectives. To that end, we will send a "dear healthcare professional" letter to the healthcare professionals described on the slide, advising them of the changes that

have been incorporated into the prescribing information for Lotronex. We anticipate that this letter will be mailed within three weeks of agreeing on the final labeling with FDA.

[Slide]

Next, I would like to describe a specific program developed to further ensure that our communications objectives are reenforced.

[Slide]

The appropriate use program is a multi-faceted program designed to convey and reenforce the communication program objectives, that being appropriate patient selection; management of constipation should it occur; and early recognitions of signs and symptoms of ischemic colitis and what recommended action should be taken. This program will utilize distinctive graphics that separate this program from other communications vehicles utilized by Glaxo Wellcome.

[Slide]

This slide lists the audiences for the program, as well as the elements of the program, and I will now describe the elements of the program in greater detail.

[Slide]

For healthcare practitioners and their office staff we will introduce the appropriate use program with an

introductory letter announcing the intent of the program and describing the individual elements of the program. Those elements are as follows: patient selection cards -- these cards contain a check list to aid healthcare practitioners in identifying the appropriate patients for Lotronex, as well as excluding patients who are inappropriate candidates. A brochure for healthcare practitioners that describes the appropriate use of Lotronex, as well as other relevant information on IBS, will also be included. A card that lists frequently asked questions, along with the answers to those questions, and, lastly, reminder items with a toll-free number to the Glaxo Wellcome medical department should the healthcare practitioner or office staff have specific questions about Lotronex that are not answered in the materials described previously.

[Slide]

This slide is an illustration of the components of the appropriate use program for healthcare practitioners and their office staff.

[Slide]

The next elements of the appropriate use program are intended for hospital and retail pharmacists. We view pharmacists as very important in communicating information about Lotronex not only to healthcare practitioners, but to patients as well. We will direct the following information

to them: An introductory letter, introducing the appropriate use program; brochures intended to be distributed to patients when prescriptions for Lotronex are dispensed. The brochure will contain information on irritable bowel syndrome, as well as to reenforce the messages around appropriate patient selection, management of constipation and the recognition of signs and symptoms of ischemic colitis, as well as what actions are recommended.

We will provide additional quantities of the patient package insert for Lotronex for distribution to patients receiving prescriptions. Pharmacists will be provided stickers to place on the prescription bottles for Lotronex which will contain important information for patients about the potential for constipation. We will also work with the major pharmacy benefits managers and pharmacy chains to install flags in computer systems that remind pharmacists to provide the patient brochure, the patient package insert and to utilize the stickers when dispensing prescriptions for Lotronex.

[Slide]

For patients, we will revise the current product sample kit distributed by physicians to patients being prescribed Lotronex. These revisions will reenforce our communications objectives for Lotronex.

[Slide]

This slide highlights the revisions to the current sample package. Firstly, we intend to place stickers on the existing sample package which direct the patient to important information contained inside the package. Secondly, we will insert an important information card inside each of the packages. The patient package insert and complete prescribing information will also be included inside each sample package, and we will provide quantities of the patient brochure described previously, along with the sample packages, to the healthcare professionals.

[Slide]

This slide indicates the type of information which will be included on the important information card for patients. These messages, once finalized and agreed upon with the FDA, will reenforce the main communication objectives of appropriate patient selection for Lotronex.

[Slide]

The sample kits will also contain a toll-free number and website address where patients can call or e-mail their acceptance to receive future mailings intended to reenforce the communication objectives described, and to receive a newsletter with information on irritable bowel syndrome.

[Slide]

This slide highlights the elements of the

appropriate use program for patients described as phase one. The reason the patient information is in two phases is that phase one provides us with the fastest method of implementing this program while we are finalizing the components that I will describe as phase two. We plan to implement phase two as soon as possible.

[Slide]

For phase two we will redesign the existing patient sample package, statistical the stickers and inserts described in phase one, and also include additional information such as a symptom diary. The symptom diary is designed to help patients in monitoring their symptoms as well as to monitor constipation if it occurs. We will also include a business reply card, offering the patients an opportunity to register for a three-wave mailing and newsletter. The patients will also be provided with a reminder item, highlighting the toll-free number and website address where they can obtain additional information about Lotronex and irritable bowel syndrome.

[Slide]

This illustration lists the enhanced phase two version of the appropriate use program for patients.

[Slide]

Next, I will describe the enhanced print and website materials. We intend to prominently display the

appropriate use information in our print as well as our website materials. These new materials will be utilized by the Glaxo Wellcome sales representatives, the customer response center which is a call center that handles all incoming calls from patients, and healthcare practitioners. This call center is located in Research Triangle Park, North Carolina.

[Slide]

We intend that these materials will also be utilized by clinical investigators, the Glaxo Wellcome medical information department and the Glaxo Wellcome speakers bureau.

[Slide]

This is a list of the materials that will be revised to prominently display the important information of appropriate patient selection, management of constipation and identification, recognition of early signs and symptoms of ischemic colitis, as well as the recommended actions.

[Slide]

The next communication vehicle will be updated information provided to healthcare practitioners who speak on behalf of Glaxo Wellcome.

[Slide]

We intend to conduct an educational program for speakers designed to highlight the important information on

appropriate patient selection. We intend to use pre- and post-meeting surveys to ensure that the healthcare practitioners who attend these programs are aware of this information and knowledge of this information will be a condition for speaking on behalf of Glaxo Wellcome in the future. Lastly, we will provide these speakers with slide kits that contain the updated information to reenforce our communications objectives.

[Slide]

The next elements of our communications vehicles will be supplemental training of the Glaxo Wellcome sales representatives.

[Slide]

For the Sales representatives we will conduct face-to-face training on the communication objectives and utilize training materials that emphasize the appropriate use messages that I have referred to previously. We also intend to implement competency testing to ensure that the sales representatives understand, and are able to effectively communicate the changes to the prescribing information for Lotronex to healthcare professionals.

[Slide]

We believe the communications program is extensive and is designed to communicate and reenforce our communication objectives for Lotronex. Next, I will

describe the evaluation approach we will utilize to monitor the communications program.

[Slide]

We intend to test our messages with the intended audiences for comprehension, as well as to track awareness and the source of knowledge to ensure that we are able to make changes as warranted in the program.

[Slide]

This slide highlights the time lines of the implementation and evaluations planned for our risk management program. We are testing comprehension of the important messages at the beginning of the program, and will establish a baseline of awareness at program implementation. We will then evaluate the program on an ongoing basis at six-month intervals.

[Slide]

We will test message comprehension with physicians, patients who have IBS, as well as pharmacists. The research will be conducted by third-party professionals utilizing standard research methodology.

[Slide]

We will also track awareness and source of knowledge by using quantitative market research. This research will be conducted by third-party professionals and will be done in four phases. The research will allow us to

test awareness in geographical segments of the United States, and will utilize consistent methodology from phase to phase. The repetitive conduct of the research will allow data to be trended and significant changes to be monitored.

[Slide]

We are very confident that the communications components, monitoring evaluation, along with the elements of the risk management strategy described by Dr. Andrews, will accomplish our intended objectives of the risk management program. We will be able to reach the intended audiences with the appropriate information and with the right frequency. This information will support the selection of appropriate patients for Lotronex, as well as identify patients who are inappropriate candidates. Lastly, the program will help to educate healthcare professionals on the safe and effective use of Lotronex.

Thank you, and I would like to bring Dr. Kent back to the podium.

Conclusion

DR. KENT: I would like to give you a brief summary of the information we have presented to you today.

[Slide]

Dr. Gralnek presented data indicating how the burden of irritable bowel syndrome compares with other serious chronic diseases. The data shows that IBS patients

have a decreased quality of life that is similar to patients with diabetes and end-stage renal disease. Patients with IBS endure significant suffering that has a large negative impact on their lives.

In my introduction I referred to FDA's position that Lotronex benefits only a relatively small number of patients. The data Dr. Mangel presented do not support such a conclusion. The efficacy data are robust. Lotronex has been shown to be effective with remarkable consistency against the most important symptoms that afflict female diarrhea-predominant IBS patients.

Many other drugs with well-accepted efficacy profiles, treating disorders with subjective endpoints and high placebo response rates, show magnitudes of benefit comparable to the magnitude of efficacy seen with Lotronex.

[Slide]

This slide shows that in a 12-week study assessing relief of pain associated with osteoarthritis, 200 mg of celecoxib achieved an incremental benefit over placebo of approximately 15 percent. Naproxen 500 mg achieved an incremental benefit over placebo of approximately 10 percent. As you are well aware, COX II inhibitors and classic NSAIDs are well accepted as efficacious therapy for chronic pain states.

[Slide]

As presented to you by Dr. Mangel, data from a recently completed study using a composite endpoint of global improvement showed a 35 percent difference between placebo and Lotronex-treated patients, favoring Lotronex. This is a robust efficacy finding.

From the totality of the available data, we conclude that Lotronex is highly efficacious and provides clinically meaningful and tangible benefits to women who suffer with the diarrhea predominant form of IBS.

[Slide]

In terms of safety, Dr. Mangel presented to you the following conclusions: There is no signal for hepatic toxicity. Cases of ischemic colitis are comparable in frequency and severity to those reported prior to approval. These cases have involved a transient, acute form of colitis. There have been no reports of sequelae. Furthermore, recently obtained data from large GI practices reveal that transient, acute ischemic colitis may be more common than previously understood.

There is a safety signal based on rare reports of complications due to constipation. These complications were not seen in the clinical trials prior to approval.

[Slide]

As presented to you today, Glaxo Wellcome has an extensive risk management program that is appropriate for

the particular risks associated with this particular medication. In addition to continued research, our risk management plan includes three elements: appropriate labeling, an effective plan to communicate new messages, and an evaluation of message comprehension and awareness.

The risk management program does not include every conceivable option. However, we believe it more than adequately addresses the risks associated with Lotronex, and is commensurate with the benefit-risk profile for Lotronex.

Let me give you an example of a risk management tool that we do not believe is appropriate based on the data, specifically, the use of a black box warning. Over the last month, we have had frequent interaction with FDA regarding modifications to the product labeling for Lotronex. While we have reached general agreement on a number of issues, FDA has suggested a black box warning for constipation and the associated rare reports of serious complications. We do not agree. We do not believe that the risks associated with this drug rise to the level normally associated with a black box warning, or that the use of black box warning would be consistent with established FDA precedent.

When we compare the benefits and risks of Lotronex against other drugs used for chronic, non-life-threatening disease states, it is clear that a black box for Lotronex

would set an unreasonable standard which may ultimately trivialize the utility of this feature of labeling. In order for prescribers to understand the information regarding warnings within context, it is important that the prominence of the information presented be consistent with established precedent. The following are examples that highlight this issue.

[Slide]

NSAID drugs, some of which are now available OTC and without a physician's guidance, are associated with a significant number of deaths and injuries each year. As illustrated by this recent evaluation from Schoenfeld, NSAIDs are associated with significant morbidity and between 10,000 and 20,000 deaths per year.

[Slide]

The information presented on this slide has been extracted from a class labeling for NSAIDs. As you can see, these agents, which are used for the treatment of chronic pain and some of which are available over-the-counter, are associated with the potential for serious, life-threatening events. Some of these events are especially troubling since heralding symptoms either do not occur or are not recognized by patients -- but these drugs are available OTC.

[Slide]

The next example provides information about other

drugs that cause constipation. We have reviewed the PDR for drugs with a recognized incidence of constipation of greater than 3 percent. We found a substantial number of agents that can cause significant serious adverse events associated with complications of constipation, including impaction, obstruction and perforation. None of these products has been required to include a black box or even a bolded warning for these events.

[Slide]

The final example raises issues about the appropriate prominence of warnings regarding fatal events described in product labeling. It also highlights FDA's views on when a boxed warning is not necessary. Sildenafil is a drug recently approved for men for a non-life-threatening condition, erectile dysfunction. A very significant drug interaction with nitrates has resulted in numerous deaths. In addition, there have also been numerous deaths associated with exertion related to coronary events in men attempting sexual intercourse. The incidence of these fatal events associated with Sildenafil is well recognized by FDA.

The labeling for this product describes the drug interaction with nitrates in the contraindication section, and the dangers related to physical exertion associated with sexual activity as a standard non-bolded warning. The FDA

has not requested a black box warning related to either of these fatal events.

[Slide]

Indeed, as reflected in this slide, quoting Dr. Janet Woodcock, the FDA specifically states that a black box warning advising against the use of Viagra and nitrates is not necessary to warn against these fatal events.

Our goal in presenting these examples is not to question other drugs but to understand the framework in which Lotronex should be labeled. We are also trying to understand from precedent how FDA applies the requirement for prominent safety warning in labeling.

As stated in my introduction, Glaxo Wellcome has proposed substantial labeling modifications which are included in your briefing materials. Glaxo Wellcome is proposing to substantially strengthen the warnings for constipation and ischemic colitis and to increase their prominence by use of bolded text. In addition, we are proposing to expand the contraindication section to identify those patients who should not use Lotronex. We believe that the labeling we have proposed is an accurate representation of the benefit-risk profile and provides essential information, with appropriate prominence, for the safe and effective use of Lotronex.

[Slide]

In summary, IBS causes real suffering in those patients afflicted. The suffering caused by IBS has a significant adverse impact on patients' lives. The data demonstrate a favorable benefit-risk profile for Lotronex. The integrated and targeted risk management plan developed for Lotronex is specific and appropriate to the product risk.

[Slide]

Mr. Chairman, that concludes our presentation. I would like to recognize a number of expert consultants who are here with us today and are prepared to respond to questions. In addition to representatives from Glaxo Wellcome, also here today are the following expert consultants who are prepared to respond to questions regarding their field of expertise: Ms. Martha Bayliss, Dr. Lawrence Brandt, Dr. William Chey, Dr. Rosemarie Fisher, Dr. Ian Gralnek, Dr. John Lennard-Jones, Dr. Rona Levy, Dr. James McGill, Dr. Louis Morris and Dr. Kay Washington. Thank you very much.

Committee Discussion

DR. HANAUER: Thank you, Dr. Kent and your group for that summary. I will now open it up to our committee for questions or discussions. Dr. Blum?

DR. BLUM: I have one question. On the 130,000 prescriptions that you mentioned as a denominator, how many

of those are refills?

DR. MANGEL: Out of the 130,000 prescriptions dispensed, that was dispensed in 115,027 new prescriptions. So, on the order of approximately 15,000 of the 130,000. So, 115,027 individual patients -- 15,000 refills.

DR. HANAUER: Dr. Surawicz?

DR. SURAWICZ: One of the cases of bloody diarrhea -- you mentioned there was one case, do you have any more information about that? That was in the additional complications that were mentioned?

DR. MANGEL: Yes, the patient had bloody diarrhea; they were scoped. They were suspicious of ischemic colitis but not calling it. The biopsy came back as normal. So, the physician thought it was some non-specific event.

DR. HANAUER: Dr. Wolfe?

DR. WOLFE: I have a question regarding the development of constipation. How many of the patients who developed constipation developed it within one to two weeks of beginning therapy?

DR. MANGEL: The median time to onset in the clinical program is on the order of ten days, and that is the median. The very vast majority of patients who do develop constipation, it is clearly within the first month. A mean is going to center around 20 days. So, within the first three weeks you clearly have many of the cases.

DR. WOLFE: There is a reason for the question. There is a lot of precedence for a phase-in, not to begin with a full dose immediately. Has any thought been given to the possibility of beginning with a lower dose and then escalating to the full dose?

DR. MANGEL: The answer is yes. As Dr. Andrews mentioned, as part of the constipation management study which we are going to do, there will be three arms. One is a laxative, one is a dose reduction and one is interruption. In addition to that, we are also thinking of a dose titration study for the reason that you said. Actually, you get reports, in the spontaneous database, in some cases very large information and in some cases very limited information and what you do see is that in several of the individuals who developed constipation the strategy that either the physician or patient takes is dose reduction.

DR. HANAUER: Dr. Ferry?

DR. FERRY: I just have a question about what is known regarding the barriers to getting both physicians' and patients' attention about these issues. I mean, we have had a major drug removed from the market recently, cisapride. An incredible attempt was made to get everybody's attention to avoid inappropriate combination of medicines, and in our own practice, we, ourselves, gave out information to patients trying to get their attention, and I just wonder

what really is known about what works best and, you know, what are the barriers to some of this.

DR. KENT: Well, just a general comment, I think if you look at the FDA's questions, I believe that is why we are here. We have proposed what we believe is a very aggressive program to try and get the information to physicians and patients, but the general question you are asking, I believe, is the reason why we are here.

DR. HANAUER: Florence, do you want to comment on that?

DR. HOUN: Well, for the cisapride lesson, I think FDA learned that multiple listings of drug contraindications, risk factors, interactions with other drugs or medical conditions contributed to the inability of people to prescribe it safely because of all these interactions and conditions you had to be aware or. So, the labeling probably was not effective and the point where we ended up with, with over 12, or 13, or 20 contraindications, at that point risk management should have changed instead of just adding more to the label.

DR. KENT: One issue on cisapride, it was on the market for a long time and many physicians probably felt incredible comfort with using it, probably making them somewhat more resistant to the type of changes FDA wanted to intervene with. We have a better opportunity with Lotronex

since it has just been on the market shortly.

DR. FERRY: I have the impression simple is better. I mean, when you give a patient a whole page of information, you know, sometimes the pertinent things really get lost. And, I am sure when we get letters as physicians with a whole page, I think it really does get lost. I think probably simpler and shorter is better.

DR. KENT: I should point out that things like "dear doctor" letter that we sent out are not simply our writing. They are reviewed and approved and sometimes edited in a heavy way by the FDA.

DR. LAINE: Do you have information, Dr. Mangel, specifically helping us decide which patients are more at risk? First of all, there are people who are just really pure diarrhea IBS patients, which are obviously a relative minority. How many of those, if any, do get severe constipation and/or ischemic colitis versus those who have, let's say, alternators? Really what I am trying to get at is a method to determine who really should get the drug and who should not get the drug.

DR. HANAUER: Before you answer that, can I pose that in a larger context that I was going to address? To frame that, when I look at the six cases of the constipation that were presented here, five out of the six patients including two that were in clinical trials had a history of

constipation as a precedent of their complication.

Yesterday and today as well, we discussed that patients were enrolled based upon Rome criteria for definition of irritable bowel, yet, we are now beginning to subgroup patients with irritable bowel into diarrhea predominant, constipation predominant and the alternators. Yet, as was presented yesterday and to this point, we haven't had a clear definition from the Rome group that it is possible to truly categorize that group of patients, that those subgroups are valid subgroups that have their own prognosis and response. So, part of the question is can we define that subgroup definitively of who would be appropriate for Lotronex?

DR. MANGEL: Any definition of either diarrhea or constipation is, of course, a population definition. What are our present definitions? They reflect a certain stool frequency over a period of time, and reflect straining versus urgency, and stool consistency. We believe the individual patient knows if they are constipated or not. The individual patient knows on the treatment if they have become constipated or not.

I think, as Dr. Laine and Dr. Hanauer pointed out, the patients who ran into trouble, or at least a goodly number of them, with respect to complications of constipation should never have been on the drug.

DR. HANAUER: But in the context of that, the revised labeling says that it would be contraindicated in patients with severe or chronic constipation. I am not certain any of the patients that had the severe complications from the drug had a previous history of severe of chronic constipation. So, I am not certain that that is identifying a risk group.

DR. MANGEL: Yes, the intent of our proposed labeling is that individuals with a history of severe constipation, individuals with a history of any type of complication of constipation, individuals who are constipated at that time should not initiate treatment. Individuals who become constipated, depending upon how they judge the severity, should either withdraw from treatment or discontinue treatment permanently and take laxatives or other measures.

I mean, this does become an important issue in terms of what does severe constipation mean. As you may recall, in our phase III program as well as phase II, individuals did call in daily on the phone system, so we had daily bowel function over the 12-week period and we actually did go back and try and reconcile, first, when a patient says they are constipated can we put objective criteria around that. In terms of stool frequency and stool consistency you really can't. You get a little better data

from the diarrhea predominant where there is some drop in consistency and frequency.

Very interesting -- we are not indicated for alternators but just relating the information, when you look at the alternators, and as a population when the alternators say they are constipated there is no change either in frequency or consistency, and I think that would correlate to some studies, for instance, by Dr. Gurwitz and Avorn in the elderly that when individuals say they are constipated you are not really necessarily seeing a change in stool frequency.

What we do see, once again as a population, is when individuals say they have severe constipation they are much, much more likely to drop out of the study. Those individuals also had a much earlier onset of their constipation. To put some numbers around that for you, those with mild constipation developed constipation after 22 days; those with severe, after 8 days. And, it is no different than mild versus severe headache. You know, what does that mean? You don't know, I don't know, but the patient knows and we believe it is the same for constipation.

DR. LAINE: What I am getting at is, in other words, is there a problem with giving it to alternators, and what timing should one use? In other words, if they have

had constipation last week, last month, last three months, do you have any information to tell us, first of all, about that or should this drug be restricted only to people who have had diarrhea and no "constipation" in the last three months, two months --?

DR. MANGEL: And, the drug, of course, is only approved for diarrhea-predominant females, one. Two, we do have an alternator study which is ongoing.

DR. LAINE: The problem though is, as we heard yesterday, diarrhea predominant, constipation predominant, still a lot of those people will actually have constipation or, you know, will have the alternate during that month, or two or three and the question is not the diarrhea predominant, the question is getting rid of the other people, in other words, the constipation people.

DR. MANGEL: Yes, in our phase three program the alternators had about an 8 percent greater rate of constipation than did diarrhea predominant. There were, once again, no increased sequelae, no increased problems in the alternators.

We do have a large alternator study, which is recruiting at present, to try and sort out the issues either, one, is there a defined alternator population that could received benefit and, two, to explore the safety profile more clearly in alternators.

DR. LAINE: But I would imagine that many of your patients who are being treated with this drug are alternators right now, and the question is how are you going to go further --

DR. MANGEL: Perhaps I can just confer our marketing colleagues. I don't know if we actually have that information in our demographics for prescriptions. Yes, we don't have a precise numerical breakdown --

DR. LAINE: But does your wording go far enough in terms of getting rid of the alternators or preventing the alternators in terms of severe or chronic constipation? I guess that is the question -- versus other wording to make it more clear or to make people with constipation even less likely to take the drug -- I guess a broader group of people who shouldn't take it related to their constipation, is what I am asking.

DR. MANGEL: Yes, and we certainly agree. Alternator who is in their constipation phase -- well, the drug should not be initiated in anybody who has constipation. The drug should not be initiated in anybody who considers their constipation severe. All of our efforts and all of our promotional efforts are strictly targeted towards our labeled indication of diarrhea-predominant patients.

DR. LAINE: I guess what I am asking is if they

have diarrhea now and they had constipation three weeks ago, is it okay for that patient to take the drug then?

DR. MANGEL: Well, what we do know --

DR. LAINE: I just think that is more real-world than, you know, they have diarrhea all the time --

DR. MANGEL: Yes. Yes, if we divide it two ways, efficacy and safety, what we do know from the phase three program is that when individuals become constipated and continue to take the medicine, i.e., do not drop out, the efficacy of those individuals is comparable to the efficacy of individuals who do not report constipation. So, from that data which we have, we would not necessarily be concerned that there is an efficacy concern.

In terms of a safety concern, all I can do is speak to the data which we have, and there were no serious reports in the clinical trials program at the time of approval. There are these six reports subsequent to approval. In three of them, clearly the individuals had what appeared to us to be a current history of constipation.

DR. LAINE: And the ischemic colitis related to the constipation issue?

DR. MANGEL: Yes, I would say no. In ischemic colitis of the seven cases in the clinical development program, three individuals had a report of constipation at some point in their history. So, that is three out of seven

or 42 percent, but you have to balance that against 27 percent in the overall clinical trials population and, you know, when you are dealing with three out of seven -- you know, I think you would not say those numbers are different for such small Ns.

In the spontaneous database, out of the five spontaneous reports, three of them actually did report constipation and, once again, is 60 percent different than 27 when you are only dealing with thousands versus five? I don't think we can comment.

Of course, the major purpose of the large 10,000 patient epidemiology study is to ferret out exactly what you are asking, Dr. Laine, to identify risk factors for ischemic colitis -- events as well as who is more likely to get constipation.

DR. KENT: Dr. Laine, let me just take a quick run-through with you of our proposed labeling with regard to constipation and see if that helps at all.

First of all, in the indications section we do say that it is indicated only for women with diarrhea predominant form of IBS. We have the Rome criteria in the appendix and we give a brief definition: diarrhea-predominant IBS is characterized by at least three months of recurrent or continuous symptoms of abdominal pain or discomfort and diarrhea, etc.

Then, in the contraindications we contraindicate in patients with a history of chronic or severe constipation or the history of sequelae from constipation. So, if anyone has chronic constipation, they are out. In addition, we contraindicate if they are currently constipated. So, if they are currently constipated they should not start the drug. In addition, if they become constipated on the drug, abd we divide it into mild, moderate and severe, and if they are severely constipated on the drug they should stop and never restart. If they have mild or moderate constipation drug holiday or treatment can be tried. If the drug holiday or treatment doesn't work, they are off and never restart. So, we think we have covered the spectrum.

In the alternator population, we are not indicated for alternators. We wouldn't promote for alternators. But if a physician had a severely affected patient and in his or her judgment wanted to use the drug in alternators, there are clear definitions of when not to start the drug and when to stop it in case it doesn't work.

DR. LAINE: I have read this already. All I am saying is that none of those address directly the alternator, which is probably the majority of people in the real-world and that is all I am asking. I mean, chronic constipation may mean to some people all the time. It is something that we can discuss later but that was really my

whole point.

DR. HANAUER: Dr. Wolfe and then Dr. Kramer.

DR. WOLFE: I actually want to take slight issue with one of the points you raised. You said that patients know whether they are having constipation or diarrhea. Don't take that for granted. We get referrals to us constantly from physicians. The patients are coming in and saying their complaint is diarrhea. When you ask them carefully, they really don't have it. So, just by putting simply diarrhea may not be sufficient to really include the proper patients to take this drug.

DR. MANGEL: My point with respect to that was actually more that we don't have any good definitions of either. Once again, you know, when we go back to our database and we look at the daily bowel function scores of individuals who, on X day, report that they have constipation, you know, you just cannot put your arms around single parameters and say this is constipation; this is diarrhea. As you see, when you look at the Rome II criteria, there are just not hard and fast definitions which apply to every individual and probably the best we can do is when a patient says they are constipated, by all means, be conservative -- if they are constipated on Lotronex they are constipated.

DR. WOLFE: Four of the patients were taking

either birth control pills or estrogens. How many of the patients were smokers?

DR. MANGEL: I believe two or three were smokers in addition.

DR. WOLFE: That may be a key too for interactions that really need to be checked. First of all, it is very easy to tell patients to stop smoking. They don't listen but it is very easy to tell them that. But if there is a predilection for thrombosis of any type, even though this not thrombotic, but if there could be an interaction in this setting they should be warned very carefully about this.

DR. MANGEL: No, we agree and, actually, we think, once again, with the large epidemiology study we will gain a lot of insight into this. For our population overall in the clinical trials program about 41 percent of the individuals were either on oral contraceptives or hormone replacements. For these cases, it is on the order of 40 or 50 percent of the individuals. You know, are those numbers different? Perhaps they will be, but we just don't have the sample size yet to say that they are, but this will be a key focus in the epidemiology study.

DR. WOLFE: There is one last issue, I also notice, looking at metabolism, your are metabolized to a fairly large extent by both 2C19 and 3A4, and I also saw two of your patients with hemorrhagic colitis actually were

taking lenzoprizole which is metabolized by 3A4. Have you done interactions looking at ACs with people taking drugs metabolized by the same route?

DR. MANGEL: Can I defer that question to our of clinical pharmacologists?

DR. WOLFE: Sure.

DR. PETER ANDREWS: We have seen some mild inhibition of the 3A4 p450, but it has been, in a clinical sense, quite a modest inhibition and we really wouldn't expect to see any sort of interaction as a consequence.

The other thing that you did say is that we see 2C19 as a principal p450 that metabolized alosetron. In actual fact it is 2C9.

DR. HANAUER: Dr. Kramer?

DR. KRAMER: Thank you. I take it as a predicate that the company does see a need for changing the insert in some way and starting the communication program and risk management program. So, with that as a predicate, and I understand from the presentation that there is an aversion to the black box solution to such a risk management program, but what I didn't hear and what would help me is an articulation of how a black box would impede the risk management program or how it would impede an educational program.

DR. KENT: Well, I think it is a matter of FDA

precedent and a level playing field for pharmaceutical companies which market drugs. On the one hand, the FDA has said in their discussions with us that they view a black box as a communication mechanism. On the other hand, we have heard that the physicians don't look at black boxes.

We don't feel, based on the examples that I gave and lots of precedent, that this drug is a dangerous drug and merits a black box and there are many other ways to communicate the appropriate data around risk-benefit. We don't believe the risk-benefit of this drug warrants a black box.

DR. KRAMER: Maybe a follow up, you presented very well the aversion to having a black box, but would it impede an educational program and a risk management program?

DR. KENT: I am not sure it would impede a risk management program, I think what it would do would be to send a message to physicians that this is a dangerous drug. I think that patients and physicians may end up making inappropriate decisions around whether to use the drug. I think there is a duty to warn that we all have; I think there is a great duty not to over-warn. We have to put the risks and benefits of all these products in proper perspective, and having a black box for this drug is not a proper perspective in our view.

DR. HANAUER: Dr. Avorn?

DR. AVORN: Thanks. I guess this is for Dr. Mangel. Although in determining efficacy FDA tends to use the minimalist and often inadequate standard of placebo comparators, you have presented data from a European study in which active comparators were used. My question is about your slide A44, comparing your product with the commonly used treatments in Europe. I noted there was no evidence or no documentation of significance in the difference. Was that an omission or was that because the difference between the product and the comparators was not statistically significant?

DR. MANGEL: Yes, for each of them we actually were significant at various of the individual weeks. Actually, our primary analysis around the adequate relief was a monthly responder. A monthly responder was prospectively defined as individuals who had at least two weeks, out of a four-week period, with adequate relief. For that analysis, missing weeks were imputed to no relief. If individuals had incompleteness in a month, then it was carried forward from the previous months. For mebeverine we had significant benefit at month two and three; for trimebutine at month three.

DR. AVORN: And not for the others?

DR. MANGEL: Yes.

DR. HANAUER: Dr. Welton, then Dr. Surawicz, then

Dr. Wolfe.

DR. WELTON: I guess I have a comment and then a couple of questions. The comment I think would be, to summarize Dr. Laine's concerns, and you actually said it best, you said it is different to put your arms around what is diarrhea and constipation in the patient. So, as the prescribing physician it is going to be very different to put our arms around what is diarrhea and constipation and how recently did that patient have that episode of not so severe constipation, just sort of mild or moderate constipation, because I am sure that nobody set out in these other patients who had constipation to give them this medication with a known history of severe complications. So, I share the concern of getting my arms around what is constipation and diarrhea in a given patient and, therefore, who would I give it to, other than somebody with a gastronoma or something like that.

I have some problems with some of the studies that are suggested. There is going to be some research done on the effect of the drug on blood vessels, cultured endothelial cells and also, as I saw in one of these stacks of papers, looking at vascular rings. Yet, in something else that I read from the November meeting, I believe, it was reported that this receptors are only in the submucosa lining in the GI tract; they are not on the blood vessels;

not on the microvasculature. So, I am not sure why we would expect to see any vascular complication of these drugs in culture endothelial cells or vascular rings. I guess I would like to understand that would be a valid tool.

DR. MANGLE: Dr. Welton, if it is okay, I could answer that question and then --

DR. WELTON: Great!

DR. MANGEL: To make it short, the endothelial cell experiment is a phase IV commitment proposed from the FDA. So, in terms of the motivation for that study, I will need to defer to the FDA as that was a phase IV commitment to us from the FDA.

In terms of the blood vessel experiment, in November we had Dr. Michael Gershon here and, you know, Dr. Gershon has looked at 5HT3 receptors -- obviously, a word expert on this who has looked at this for years, and 5HT3 receptors -- he does not identify them directly in the smooth muscle themselves, just as you are saying, sir. What we still want to do, you know, if this ischemic colitis is being caused by Lotronex, we need to dissect out where this could be occurring. You know, is this a direct mucosal toxin? As we pointed out in our briefing document, we go back and re-review our high dose animal studies in which animals receive many, many-fold the dose for up to periods of two years and there are no lesions noted. We then looked

at blood flow in vivo in rat and there was no effect in rat on the mesenteric blood flow. We also wanted to see if this could be a direct vasospasm and is it a species difference, and that is why the studies on the mesenteric arteries and its major branches were done, and we see no effect on contractile activity. Of course, those arteries don't show rhythmic contraction but there is no effect on spontaneous tone and there is no effect on the amplitude of neuronally induced contractions. Then, this was the motivation and, once again, is this a species difference, and this is the motivation for doing the PET scan study in humans to see if there is a change in mesenteric blood flow in humans with alosetron. Once again, we are just trying to understand the mechanism of how this could be occurring.

DR. WELTON: I understand the motivation behind it. I am just not sure that the studies will show us anything because of receptor specificity, different tissue types and the preliminary data, that was at least presented in November, that shows there are no receptors there. So, you will look for a response there and you won't get a response there which will be predictable. So, we are looking at the wrong level. Maybe it is a dilatation of a bowel --

DR. HANAUER: So, your recommendations are? Tell them what to do.

DR. WELTON: I just want to understand in your two patients with constipation, just so I understand, one patient had a colectomy, an ileostomy, then a subsequent operation to close that ileostomy or has that been done? Then, finally, in the patient who had the sigmoid perforation, it was mentioned in the papers I read beforehand that that perforation was repaired, and it was mentioned this morning that that perforation was drained. I just want to understand was there a colectomy and colostomy or was there just a drainage?

DR. MANGE: No, in the 70-year old female that had the perforation, it was repaired. As of the latest information we have on that one case, we don't know if there is re-anastomosis.

DR. WELTON: So, the colonic perforation with inter-bowel contamination and pericolonic abscess was repaired and drained.

DR. MANGEL: That is my understanding, yes.

DR. HANAUER: Thank you. Yes, we share your concern that we don't really have diagnoses on many of these patients, ultimate diagnoses.

DR. SURAWICZ: I have a couple of comments. While there have not been any deaths with the complications, certainly my feeling is that the complications are serious, and the 72-year old woman with the bowel perforation in her

rectum -- I think it is terrific that she didn't die but I think it probably luck and good medical care. So, while we don't understand what is happening with the complications, certainly it seems that the drug does cause ischemic colitis and does cause constipation severe enough to cause complications that most of us don't see in our constipated patients very frequently.

Thus, your communication program and your risk management program is really important and, while I am impressed with the breadth of types of things that you are doing, it strikes me that it is really based on a part of the population -- I think of my own population of patients in a county hospital where patients are from Asia and North Africa and the Ukraine, and I think you are really going to need to develop ways to communicate with those types of patients -- not only language barriers but also simplicity. Web-based materials wouldn't help my patient population at all.

So, I think you really have a chance to be leaders and to develop innovative ways to communicate not only with patients but also with physicians, and to perhaps become leaders and do something really terrific and look at ways so that all other drug companies could follow your lead if you could develop even better ways to communicate.

DR. KENT: I will make a comment and then ask Mr.

Hull to make a comment on the communication. We agree that the individual cases represent serious complications. When we look at the signal in its entirety, we are not sure where to place it. We don't believe, again in the spectrum of examples that I gave you, this signal does not seem to stand out.

If you review the PDR for drugs currently used, as far as we understand, ineffective drugs for the treatment of IBS that can cause constipation, and listed in the PDR are the same complications of constipation that we have seen. We have a drug that has proven efficacy and has actual data and, again, compared to the examples that I gave, if Lotronex is as dangerous as you are presenting it to be, then non-steroidals have to be pulled off the U.S. OTC market -- 10,000 to 20,000 deaths per year, well documented by the CDC.

DR. HANAUER: We understand your balance but we are asked here how to manage --

DR. KENT: I understand that. I am trying to bring it back constantly to the context --

DR. HANAUER: We understand that --

DR. KENT: Because I think it is very easy to say, well, this case was very serious; this patient could have died --

DR. HANAUER: Yes.

DR. KENT: And, you know, when we get up to a million prescriptions I am sure we will have a death. I am sure that will happen. We have to place it in context. Do you want Mr. Hull to respond to the communication issue that you raised?

DR. WOLFE: Before he does, let me say one thing. I actually wanted to make the same comment, just to go a little bit further. Even for those that are in English, what level of education are you going to be aiming at?

MR. HULL: I appreciate the suggestions by the committee and I wanted to reenforce that not only is simplicity one of the main messages that we would like to get across in our communication vehicles, but we will consider utilizing multiple different language formats to address the different ethnic populations that we are seeing in gastrointestinal and family practitioner practices.

DR. HANAUER: Dr. Blum and then Dr. Kramer.

DR. BLUM: Yes, one of the comment I have is that we are getting hard data on a very loose definition on what diarrhea is and what constipation consists of, but what we are really talking about here is a patient-defined disease. Am I constipated or do I have diarrhea? And with that in mind, shouldn't the education really be going to the patient, in the patient package insert or medication guide, where the patient would sign off on the bottom I understand