FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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JOINT MEETING

OF THE

NONPRESCRIPTION DRUGS AND GASTROINTESTINAL DRUGS

ADVISORY COMMITTEES

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Friday, October 20, 2000

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The meeting was held at the Holiday Inn Gaithersburg, Two Montgomery Village Avenue, Gaithersburg, Maryland 20879, at 8:00 a.m., Eric P. Brass, M.C., Ph.D., Chairman of NDAC, presiding.

PRESENT:

ERIC P. BRASS, M.D., Ph.D., NDAC Chairman

GEORGE A. BLEWITT, M.D., NDAC Industry Liaison (non-voting)

LOUIS R. CANTILENA, JR., M.D., Ph.D., NDAC Member

SIDNEY COHEN, M.D., GIDAC Guest (non-voting)

SUSAN COHEN, NDAC Consumer Representative (non-voting)

RALPH D'AGOSTINO, Ph.D., NDAC Consultant (voting)

GEORGE DOUGLAS, Ph.D., GIDAC Guest (non-voting)

PRESENT (Continued):

JANET ELASHOFF, Ph.D., NDAC Consultant (voting)

NANCY L. GELLER, Ph.D., GIDAC Member

EDWIN E. GILLIAM, Ph.D., NDAC Member

JULIE A. JOHNSON, Pharm.D., NDAC Member

Y.W. FRANCIS LAM, Pharm. D., NDAC Member

JON MIRSALIS, Ph.D., GIDAC Guest (non-voting)

RICHARD A. NEILL, M.D., NDACA Member

MALCOLM ROBINSON, M.D., GIDAC Guest (non-voting)

GEORGE SACHS, M.D., GIDAC Guest (non-voting)

HARI C. SACHS, M.D., NDAC Member

SAMUEL SHAPIRO, M.B.B.CH., MRCP, NDAC Consultant (voting)

MARVIN M. SHUSTER, M.D., GIDAC Guest (non-voting)

WILLIAM M. STEINBERG, M.D., GIDAC Member

DONALD L. UDEN, Pharm.D., NDAC Member

HELGE L. WALDUM, M.D., GIDAC Guest (non-voting)

SANDRA TITUS, Ph.D., NDAC Executive Secretary

SPONSOR REPRESENTATIVES:

DOUGLAS Ws. BIERER, Ph.D., Procter & Gamble

TOMMY ANDERSON, Ph.D.

DONALD O. CASTELL, M.D., Graduate Hospital

LEWIS KINTER, Ph.D.

DOUGLAS LEVINE, M.D., AstraZeneca, L.P.

SPONSOR REPRESENTATIVES (Continued):

BRIAN REID

BERNARD P. SCHACHTEL, M.D., Yale University School of Medicine

NORA ZORICH, M.D., Ph.D., Procter & Gamble

FDA REPRESENTATIVES:

MARK AVIGAN, M.D., DGCEDP

LING CHIN, M.D., M.P.H., DOTCDP

JASPI CHOUDARY, B.V.Sc., Ph.D., DGCDP

JOSEPH DeGEORGE, Ph.D., DGCDP

ROBERT DeLAP, M.D.

CHARLES GANLEY, M.D., DOTCDP

LARRY GOLDKIND, M.D., DGCDP

LINDA KATZ, M.D., DOTCDP

KAREN LECHTER, J.D., Ph.D., DDMAC

VICTOR RACZKOWSKI, M.D., ODE III

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

(8:03 a.m.)

CHAIRMAN BRASS: Good morning. I'm Eric Brass. I'd like to welcome you all to this joint meeting of the Nonprescription Drug and Gastrointestinal Advisory Committees to consider the approval of Prilosec or omeprazole.

We have a number of guests with us today. So I'd like to begin by just going around the table allowing everybody to introduce themselves. This will also be microphone practice. Please be sure to turn on the microphone when you speak and to turn it off when you're done so that miscellaneous remarks don't get broadcast throughout the room.

Perhaps we could being with Dr. Mirsalis.

DR. MIRSALIS: I'm Jon Mirsalis, Director of Toxicology at SRI International in Menlo Park, California.

DR. GEORGE SACHS: This way?

I'm George Sachs, physiology and medicine, UCLA.

DR. ROBINSON: I'm Dr. Malcolm Robinson at the Oklahoma Foundation for Digestive Research at the University of Oklahoma Health Sciences Center.

DR. BLEWITT: George Blewitt, industry

representative for NDAC.

DR. DOUGLAS: I'm George Douglas. I'm head of the Mutagenesis Section, Department of Health in Canada.

DR. WALDUM: Helge Waldum, professor of gastroenterology, Trondheim, Norway.

DR. SHAPIRO: Samuel Shapiro, emeritus Director of the Sloan Epidemiology Unit at Boston University.

DR. SHUSTER: Marvin Shuster, gastroenterologist and professor emeritus of medicine and psychiatry at Johns Hopkins University School of Medicine.

DR. COHEN: Sidney Cohen, gastroenterologist, Chairman of Medicine at Temple University School of Medicine in Philadelphia.

DR. STEINBERG: William Steinberg. I'm a gastroenterologist in private practice in Washington, D.C.

MS. COHEN: I'm Susan Cohen, the consumer representative.

DR. GILLIAM: I'm Edwin Gilliam a family nurse practitioner from Tucson, Arizona on the NDAC Committee.

DR. TITUS: I'm Sandy Titus. I'm the

Administrator for the Nonprescription Drugs Advisory Committee. I'm with the FDA.

DR. CANTILENA: Yes. I am Lou Cantilena, head of clinical pharmacology at the Uniform Services University.

DR. ELASHOFF: Janet Elashoff, biostatistics, UCLA and Cedar Sinai.

DR. GELLER: Nancy Geller. I'm the Director of Office of Biostatistics Research at the National Heart, Lung, and Blood Institute in Bethesda.

DR. UDEN: I'm Don Uden, University of Minnesota, member of NDAC.

DR. JOHNSON: Julie Johnson, University of Florida, member of NDAC.

DR. D'AGOSTINO: Ralph D'Agostino, Boston University, biostatistician.

DR. LAM: Francis Lam, University of Texas Health Science Center in San Antonio, a member of NDAC.

DR. NEILL: Richard Neill, a family physician and faculty member from the University of Pennsylvania.

DR. KATZ: Linda Katz, Deputy Director from the Division of Over-the-counter Drug Products at the FDA.

DR. GANLEY: Charlie Ganley, Director of Division of Over-the-counter Drug Products, FDA.

DR. RACZKOWSKI: I'm Victor Raczkowski, Deputy Director in the Office of Drug Evaluation III, at the FDA.

CHAIRMAN BRASS: Thank you.

I'll now ask Dr. Titus to review the conflict of interest statement.

DR. TITUS: The following announcement addresses the issue of conflict of interest 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 the 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 Drs. Eric Brass, Ralph D'Agostino, Edward Krenzelok, Hari Sachs, William Steinberg, and Ms. Susan Cohen.

Copies of these waiver statements may be

obtained by submitting a written request to FDA's Freedom of Information Office, located in Room 12A30 of the Parklawn Building.

In addition, we would like to disclose for the record that Dr. Francis Lam has an interest which does not constitute a financial interest within the meaning of 18 USC 208(a), but which could create the appearance of a conflict. The agency has determined notwithstanding this interest that the interest of the government in his participation outweighs the concern that the integrity of the agency's programs and operations may be questioned. Therefore, Dr. Lam may participate in today's discussion of Prilosec.

We would also like to note for the record that Dr. George Blewitt is the non-voting industry representative and is on the Nonprescription Drugs Advisory Committee to represent industry interests. As such, he has not been screened for any conflict of interest.

With respect to FDA's invited guests, their reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Marvin M. Shuster would like to disclose for the record that he has in the past served

as a consultant to Glaxo Wellcome, Janssen, and Tap Pharmaceutical.

Dr. Shuster would also like to disclose that he is retired from Janssen Pharmaceutical.

Dr. Helge Waldum would like to report that --

DR. SHUSTER: Could I correct that, please? I am professor, the Janssen-Strauss-Hallbright Professor of Medicine emeritus. So I'm a former professor of medicine, which was co-sponsored by Janssen.

DR. TITUS: Thank you.

Dr. Helge Waldum would like to report that his daughter is employed by AstraZeneca.

Dr. George Sachs would like to report the following interests. He consults for AstraZeneca, Wyeth Ayerst, Byk Gulden, Eisai-Janssen, and Takeda Abbott. He also serves as a speaker for Wyeth Ayerst and Eisai-Janssen.

Dr. Sachs has also reviewed and served as a scientific advisory on omeprazole, lansoprazole, pantoprazole, and rabeprazone.

Dr. Sidney Cohen reports that he has given individual talks, performed research studies, and consulting on omeprazole and lansoprazole.

Dr. Jon Mirsalis reports that he has in the past performed work for SmithKline Beecham, Procter & Gamble, Merck, and Tap Pharmaceutical. Dr. Mirsalis has also served as an expert on a review panel for lansoprazole in the early 1990s.

Finally, Dr. Mirsalis reports that he served on an advisory panel for Tap Pharmaceutical on the toxicity of omeprazole and lansoprazole.

Dr. Malcolm Robinson reports that he has served as a consultant and speaker for firms that manufacture H2 receptor antagonists. Dr. Robinson has spoken most recently for Janssen Pharmaceutical.

Lastly, Dr. Robinson has served as an investigator for Johnson & Johnson, Tap, Wyeth Ayerst, AstraZeneca, Eli Lilly, SmithKline Beecham, and Procter & Gamble.

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 all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any

first whose products they may wish to comment upon.

CHAIRMAN BRASS: Thank you.

Yes, sir.

DR. SHAPIRO: Some time in the past -- I can't remember when -- I performed a study of Astra.

CHAIRMAN BRASS: Thank you.

I will also note that anyone who is interested in participating in the open public hearing this afternoon, please be sure to register at the information desk in front.

I'll now turn the floor over to Dr. Charles Ganley to introduce the issues for today's discussion.

DR. GANLEY: Yeah, I'm just going to be very brief about this so that we can get on with the meeting. I know there's a lot of information to go over, and what I want to do is just try to focus the committees on what the differences are in views between the sponsor and the agency.

The Advisory Committee will review the data to support the use of Prilosec for the treatment of heartburn in the over-the-counter market.

There are some differences of opinion between the sponsor and FDA review divisions in the interpretation of the data, the efficacy data,

particularly the data pertaining to the acute relief symptom, the acute relieve of symptoms and how this product is likely to be used in the OTC market.

I think you'll see these distinctions as we go through the presentations, and the one concern of the FDA is how the product is likely to be used, and that individuals with gastroesophageal reflux disease may be actually using this product in the over-the-counter market, and we don't really take a view on this.

We actually want the opinion of the committees of whether this is an appropriate treatment, and if it is an appropriate treatment, is the product appropriately labeled for that?

I think I'll leave it at that for now and get started with the discussion.

CHAIRMAN BRASS: Thank you.

We will now turn the floor over to the sponsors for their presentation, which I understand will be coordinated by Dr. Bierer.

DR. BIERER: Ladies and gentlemen, the Advisory Committees, and members of the Food and Drug Administration, good morning. My colleagues and I are pleased to be here today to present the data that supports the new drug application for the Rx to OTC

switch of omeprazole magnesium.

My name is Doug Bierer, and I have the regulatory responsibility of Procter & Gamble for this product, which is a collaborative effort between AstraZeneca and the Procter & Gamble Companies.

The purpose of our presentation today will be to show you that omeprazole magnesium is an excellent candidate to be switched from Rx to OTC status.

In our NDA, we studied two indications: the relief of and prevention of heartburn, acid indigestion, and sour stomach. We also studied two doses. We studied the lowest Rx dose, 20 milligrams, and half of the lowest Rx dose, ten milligrams.

When we began our program about four years ago, we based our program on existing H2 receptor antagonist paradigms and models. We have learned a lot since then, and we want to share this learning with you during our presentations today.

Omeprazole has been marketed for over 12 years and is approved for eight indications at doses ranging from 20 to 80 milligrams. Recently both ten milligrams and 20 milligrams were switched from Rx to OTC status for the treatment of heartburn in Sweden.

Omeprazole is currently available in more

than 100 countries and today more than 380 million patient treatments have been used worldwide.

In our program we conduct an extensive clinical program to understand the safety and efficacy of the product. In addition, we conducted an extensive consumer research program to broaden our understandings of consumers' needs and how they use the products. And our presentation today will show the results of this.

There has been a steady evolution in the OTC heartburn management. It started with antacids for the symptomatic relief of heartburn systems.

Next, H2 antagonists added prevention, which is prevention before provocative meal.

And now we're looking at a new entry into the OTC heartburn management, which is omeprazole proton pump inhibitor.

We believe that omeprazole provides a new level of benefit, 24 hour protection with the convenience of a single tablet. And this will extend the existing continuum of heartburn management.

What I'd now like to turn to is how consumers use -- what their heartburn is, how they use medications, and also their interactions with physicians.

In the consumer research that we conducted, we found that 40 percent of U.S. adults currently experience heartburn, quite a common ailment, and of those, 46 percent have heartburn that occurs once a week or more. That's more than 50 million consumers.

And of the consumers that use OTC H2 receptor antagonists, they generally suffer a frequency of heartburn about 2.4 times per week, and of those, 58 percent of the H2 users suffer heartburn on two or more consecutive days during the week.

Thus, many OTC heartburn consumers have frequent heartburn.

People who have heartburn also use OTC medications to manage their heartburn. In fact, 77 percent of them use OTC medications, and the medications that they use ar basically antacids, 80 percent, or H2 receptor antagonists, 64 percent.

And the reason this adds up to more than 100 percent is that several times H2 users will use an antacid product to supplement their medication regimen. OTC medicines are used for both relief and prevention of heartburn. In fact, we found that 26 percent of OTC H2 users used it preventatively.

There is a question of whether people who

are using H2 products actually see their physician or speak with them. In the research that we conducted in more than 2,000 OTC consumer users, we found that 60 percent of them who suffer heartburn consult with a physician or a pharmacist. In fact, those people who have heartburn greater than once a week, 79 percent of them seek physician advice.

And when those people do see their physician, more than 60 percent of them have a recommendation for an OTC medication. This raises a question of whether the people that in switching a drug from Rx to OTC, whether that will actually keep people from seeing their physician, and we studied that in the following ways.

We wanted to understand whether the H2 antagonist from Rx to OTCs actually resulted in less physician visits. Let's look at the data.

The first evidence comes from studies that are two published studies and one study that we conducted ourselves. The first was from the Fallon Clinic involving more than 2,000 patients with acid related conditions, and that study reported there was no change in the number of doctor visits before and after the switch of H2 receptor antagonists.

Second, the Minneapolis consumer survey

conducted by Dr. Shaw showed there was no change in the mean number of doctor visits before and after the switch of H2s.

And in the study that we conducted looking at administrative claims of move than 7,000 patient records, we found that the number actually increased of doctor visits for heartburn, dyspepsia, and reflux. So the data supports that with the switch of Rx to OTC, especially of the H2, that there was no change in the number of physician visits.

We believe that physician visits and seeking professional help is important, and we want to emphasize this with our labeling and our consumer education program.

Despite the fact that OTC products are widely available, both the H2 antagonists and the antacids, we found that there are definite unmet consumer needs, and this involves, first, a lack of all day efficacy and symptom breakthrough. We found that many people need to take more than one product a day in order to control their heartburn.

Sixty-three percent of antacids take more than two doses a day, and the number is 42 percent among the H2 users.

Also, they use multiple therapies to

control their heartburn. With people that are taking daily H2s, also 74 percent take an antacid product two or more times a week in order to control their heartburn, and they do this either before, during, or after they have taken their H2 product, and also consumers do want the convenience of dosing.

In looking at this, we wanted to find out and discover who are the consumers who will benefit from the OTC use of omeprazole. These are adult users of OTC products. They're also the consumers who use heartburn medications preventively and also consumers who have heartburn more than one time a week and use OTC medications. This is the OTC population that we are seeking for OTC omeprazole.

Even with the unmet consumer needs, we find that many consumers are still looking for ways to control their heartburn, and we believe that omeprazole magnesium provides a solution for this by providing 24 hour duration of effect, complete prevention of symptoms with the convenience of a single tablet.

In considering the switch of omeprazole to OTC status, we evaluated our data against six key criteria. There are:

The appropriateness of the omeprazole for

the OTC management of heartburn;

The effectiveness of the doses under consideration;

Whether the ability of consumers to comprehend the label instructions and to use the product appropriately;

The safety for use in an OTC setting;

The benefits of OTC use outweighing potential risk;

And, finally, the appropriately labeled for a consumer use.

During our presentation today, we will show you that we have met each of these criteria.

With this, I'd like to introduce the flow of our presentation today. First, Dr. Don Castell will talk about heartburn management and where omeprazole fits into the OTC use of that.

Next, Dr. Nora Zorich will review our extensive clinical data showing that the strength of omeprazole is in treating and preventing heartburn.

Next, Dr. Bernard Schachtel will review the consumer use studies and also our label comprehension studies.

Next, Dr. Douglas Levine will review our vast amount of safety data with omeprazole, showing

that omeprazole is safe for OTC use.

And finally, Dr. Nora Zorich will show us how with appropriately labeling omeprazole is an excellent candidate to be marketed as an OTC product.

We are confident that the data we will now present demonstrates that omeprazole is both safe and effective for the use in an OTC setting, and now I'd like to introduce Dr. Don Castell.

DR. CASTELL: Good morning, everyone. Can you hear this in the back? Oh, now you can hear it in the back.

It's nice to be here with you. My name is Con Castell, and as you heard, I'm the Chairman of Medicine at the Graduate Hospital. More importantly, I'm a gastroenterologist, and I hesitate to tell you this, but I have been one for over 30 years.

And during that time, I have focused my interest primarily on the esophagus, both clinical and research interests. People call me an esophagologist, and perhaps I should define that term for those of you that are not familiar with it. That's best defined as an individual who makes a living out of heartburn, whereas most folks have heartburn from making a living. And even though that's amusing, that's exactly what we have done.

We esophagologists have studied these patients with heartburn as a symptom of gastroesophageal reflux, and again, let me define that term for you, if I might.

We esophagologists tend to use the term "gastroesophageal reflux disease," or GERD, as many of you know. It's become very popular. The definition that most of us subscribe to is that this is basically the symptoms that are produced by the reflux of gastric contents, primarily acetic gastric contents, into the esophagus with or without the presence of esophageal mucosal damage or esophagitis.

And one of the points that I will try to leave you with today is that this symptom of heartburn pervades the entire spectrum of GERD.

Now, thinking about the potential for an over-the-counter switch for a very effective drug like omeprazole, a number of questions, I think, need to be dealt with. I've listed them here for you.

When is heartburn not GERD?

What is the prevalence of this condition? We've heard a little bit of that already.

Which patients are candidates for the potential OTC switch of a PPI?

Is long-term PPI use safe?

And perhaps the most important question: would an OTC proton pump inhibitor use mask an important disease?

Let me try to deal with these. Here you see a perspective on the so-called GERD iceberg. Now, I have to tell you that 15 years ago we published this in a very obscure publication, but for some reason it has a life of its own and it keeps recurring.

But the concept that was developed at the time was to try to give a perspective on how reflux disease presents in the population. Underneath the water line, which would be somewhere here perhaps, are a large group of patients that treat themselves over the counter. You've heard some about that. You're going to hear more about that today.

And they treat themselves with life style in various over-the-counter medications. Somewhere up here, we could draw a line, and now the physicians begin to interact, and usually the primary care physicians using therapies, such as proton pump inhibitors and prescription H2 blockers.

We gastroenterologists and esophagologists are more likely to see the patients up here at the tip of the iceberg. The difference in where people are on this iceberg basically relates to the chronicity or

persistence of their symptoms, and that symptoms is heartburn.

You heard these data already. So I will very quickly go through this. This is from a study we performed again almost 24 years ago in 1,000 individuals where we simply asked do they have heartburn and how often. What precipitates it, et cetera?

And as the slide shows, about 11 percent of the U.S. adults have heartburn every day, about 13 percent on a weekly basis, and about 18 percent on a monthly basis for a total of about 42 percent. This is a common condition.

More importantly perhaps is what do we find when we endoscope a patient with heartburn? This then being the endoscopic spectrum of GERD, heartburn being the symptom that brings the patient to the physician.

Approximately half of the time we do not find any evidence of injury, that is, there's no esophagitis. Some people would call that innocent GERD, but GERD nonetheless.

Forty percent of patients will find some evidence of esophageal erosive disease, and roughly ten percent of individuals will find evidence of

Barrett's esophagus. Now, that's a metaplastic change in the lining. That's, I would argue, the important condition that people are worrying about masking when they consider over-the-counter treatment.

And then this little slice here says that about one half a percent of patients with Barrett's per year are likely to develop adenocarcinoma of the esophagus, or cancer of the esophagus.

I think that this observation is a very important one that summarizes what's been known for some time. It, however, happens to be a very recent one, published just two months ago by these investigators out of Duke University, and they've compared roughly 100 individuals with Barrett's esophagus. That's the yellow bars, and patients with otherwise uncomplicated GERD, with or without esophagitis. That's the blue-green bars here.

And they looked at the severity of reflux symptoms, that is, heartburn, and what they found was that they could not predict whether the patient was a Barrett's patient or an uncomplicated GERD patient based on the presentation. The severe symptoms were just as likely in both groups.

And, in fact, mild heartburn was more likely in patients with Barrett's esophagus than in

patients of uncomplicated GERD. Now, we've known this a long time, but when you have the metaplasia to the lining of the esophagus, you lose the sensitivity to the ongoing acid exposure.

So one could argue that if we're worried about masking Barrett's with a more potent acid suppressing drug, that we are potentially already doing that with the over-the-counter products that are already out there because many of these people have mild symptoms and will respond to an H2 receptor antagonist.

What about heartburn and GERD then? I would argue with you that heartburn is the typical symptom of GERD. The symptoms have been shown to correlate poorly with the level of tissue damage, particularly the Barrett's, as I discussed.

GERD usually recurs after effective treatment. That is, we see it as a chronic condition.

Now, let's talk about the risk for just a minute. And, again, I try to bring to you the most recent comment that I could find in the literature, again, in the year 2000 by John Dent and colleagues, a very well respected international esophagologist, if you will.

And Dent said in this particular

publication the substantial data that now exists from long term treatment of humans with proton pump inhibitors has not thus far revealed any definitive risks.

Then he went on to say as a little barb to our surgical colleagues the risk of death from anti-reflux surgery, although small, would seem to far exceed any possible risk associated with long-term proton pump inhibitor use.

Perhaps more important, the studies out of Amsterdam by Ellie Klinkenberg and her colleagues, published in Gastroenterology, again, in this year 230 patients with continuous prescription treatment with omeprazole for 11 years and doses ranging from 20 up to 120 milligrams a day.

Yearly endoscopy looking for histologic changes in the gastric fundus. After 1,500 patient-years of follow-up, no serious adverse side effects have been seen. This is the longest continuous observation of any series of patients worldwide.

Conclusions then, coming back to the questions that I posed at the beginning. What is the relationship for heartburn and GERD? Heartburn is the symptom throughout the spectrum of GERD. I don't believe you can separate the two, and any kind of

separation I think is artificial.

What is the prevalence? Roughly 42 percent of the population has heartburn some of the time.

Who then do I think might be candidates for over-the-counter omeprazole? I think those patients that can use it for the prevention of predictable heartburn, and perhaps it's time to let the consumer be involved in the management of their heartburn.

And then finally, what about safety? I think the safety of long-term omeprazole is well established. What about masking of an important disease, particularly Barrett's? I think that it's unlike, if properly labeled, and in fact, I would argue that, again, if properly labeled, it may actually bring more heartburn patients to doctors rather than less.

Thank you very much for your attention.

DR. ZORICH: Good morning. My name is Nora Zorich. I'm a Medical Director of Procter & Gamble Pharmaceutics.

I'm going to take you through a brief review of the efficacy data in support of the treatment and prevention of heartburn using

omeprazole.

There are really just two topics I'll talk about. Very briefly we'll cover some basic pharmacokinetic and pharmacodynamic parameters relative to the application of omeprazole for over-the-counter use, and then I'll turn to the efficacy trials.

Here's the pharmacokinetic data shown by the drug plasma concentrations in people taking 20 milligrams omeprazole magnesium. This is with the MUPS, the multi-unit pellet system, which is the dose form that's intended for market use in OTC.

What I'd like you to see here is that the time to maximum plasma level is about an hour and a half, ranging from one to two and a half hours.

Relative to the pharmacodynamic behavior, this slide shows the dose dependent inhibition of pentagastrin stimulated adzes secretion after single doses of both 20 and 40 milligrams omeprazole. In this model you see the greatest magnitude of effect within about one or two hours after the dosing.

Now, omeprazole binds to the proton pump and inactivates it. This slide demonstrates the duration of action over time. What you see is the length of effect reflects the appearance of new proton

pumps over the subsequent few days. I think you can see that after 24 hours about 50 percent of the baseline acid output is restored. The acid inhibition effect then is essentially gone over the subsequent several days.

In this model, 20 milligrams was not different from placebo after three days from the initial dose.

The omeprazole program has two components, as Dr. Bierer mentioned. I'm going to talk about the efficacy program, and after my talk, Dr. Schachtel will tell you about the use trials. So that's where the overall program then has over 11,600 people in the clinical studies.

Let's look in greater detail now at the efficacy program. This is kind of a road map for my talk, and what you'll see is over about 9,300 consumers were enrolled in both studies looking at prevention and treatment, and you can see altogether there are six studies in the clinical efficacy program.

The prevention program is what I'll talk about first. And there are two studies which looked at the model that had been previously used in the H2 receptor antagonist switches, and that's one hour

before a meal the product is taken.

Then there are two unique studies that have never been done before, and these were specifically designed to investigate the duration of action of omeprazole. These studies assessed 24 hour heartburn prevention with people taking omeprazole in the morning for 14 days.

And then the treatment studies I'll talk about next, and you can see there are two of those studies which are 14 days in length.

Now, before I go into individual studies, I want to talk about some common features across the entire program of six studies. How were these consumers identified? This is a very important question.

The majority of the people who participated in these trials were, in fact, recruited through a national, which is coast to coast, advertising campaign, which included television, radio, and mail flyers. The respondents self-identified to the simple question do you have heartburn, and there was no further specification or any understanding of the attributes of their heartburn at that time.

Now, once the consumers were identified as

potential participants, then they could enter into a screening phase in which subjects had to have more appropriate criteria with respect to their heartburn history.

Now, we enrolled people with mild to moderate uncomplicated heartburn and excluded people who we thought would be better served under the care of a treating physician. In order to understand that, let's look specifically at some of the key inclusion/exclusion criteria.

The participants had to have uncomplicated heartburn, and as such, one of the inclusion criteria is that they had controllable heartburn, and what we mean by that is that they had said that in the past, they were able to manage their heartburn using over-the-counter products.

Specifically we excluded people who said that they only could manage their heartburn if they took an over-the-counter product every day. We also specifically excluded anyone who had been evaluated for the complications of acid reflux disease. So these are people who had a diagnosis of GERD, erosive esophagitis or any other complication of acid reflux.

Now, as is standard for heartburn studies, we enrolled people who had heartburn at levels enough

that we could measure it. So we recruited people who said by history, by recall that they had had heartburn at least twice a week in the month prior to their participation.

Once people went through this screening phase, they entered the qualifying phase, and in that one week run-in period, we documented that, indeed, they did have heartburn at least twice, and we also wanted to make sure that they were correctly filling out the forms.

Once they moved through these two phases, they could be enrolled in the actual clinical studies.

Now, I'm going to in the interest of time just summarize for you the demographics across the entire six studies. I think what you'll notice here is that if you were to look at across the U.S. census, that these people, in fact, are very representative of the U.S. population in general, and not surprising for people enrolled in heartburn studies, their weight is a little high, about 190 pounds. There's a decent amount of use of tobacco, alcohol, and just about everybody consumes caffeine.

Now, again, back to our road map. Let's first talk about these 24 hour prevention trials, and as I said, there were two identical trials. These

trials represent the first of their kind to demonstrate all day heartburn prevention with a single dose. People received either placebo, ten or 20 milligrams, which is a common dosing throughout all six studies. Since these people were not housed in the study setting and were not given any of the means, the heartburn they were having was heartburn caused by their usual lifestyle and their usual meals.

Gelucil, an antacid, was provided if they felt they needed additional relief, and the use of this was monitored.

These trials looked at the prevention of heartburn for a full 24 hours, including the assessment of nighttime heartburn, and that's why we elected to dose in the morning.

The first slide I'm going to show you is 24 hour prevention after the very first dose. Because it's a single dose, plotting on the Y axis are the percent of subjects heartburn free. As I said, there's two identical studies, 171 and 183, and what you'll see across both doses, ten and 20 milligrams omeprazole, there are significant differences compared to placebo. This was the primary endpoint of this trial.

Next, we'll look at the results over the

entire 14-day period. Now, because it's 14 days, I'm looking at the percent of days heartburn free. When all episodes are considered over the entire study period, omeprazole at both ten and 20 milligrams provided a higher percentage of days with complete prevention of heartburn versus placebo. You could see very small P values.

Now, 20 is numerically superior to ten in these trials, in both of the trials, but I think it's important to note that ten was also statistically significantly superior to placebo, and in Study 171 very comparable to 20.

Now, at the end of the 14 days all subjects were switched to daily doses of placebo. This follow-on phase was an important element of the study, as we wanted to know what would happen once the drug was discontinued.

The vertical axis here I'm plotting the percent of subjects with no heartburn and day zero would be the last day that they took active study drug. Then they were all provided placebo, but the study remained double blind.

The lines represent the daily incidence of heartburn within the medication groups, and you can see that the heartburn symptoms begin to recur one day

after omeprazole was discontinued. These results are consistent with the pharmacodynamic data that we just reviewed, showing that the inhibition of gastric acid secretion by omeprazole is maximal for the first 24 hours, and then the effect diminishing over the next two to three days.

Back to the road map, we'll now look at the one hour meal induced trials. As I said, this was the model employed by the over-the-counter H2 receptor antagonist in their switch programs, and these are very comparable to those studies, except that we modified the primary endpoint and enhanced it by employing a very stringent criteria for efficacy, which I'll discuss.

Now, in contrast to the previous studies, these are single dose, the same dose as ten and 20 milligram omeprazole, and the subjects are dosed one hour before the provocative meal, and rescue medication use was also monitored.

As I mentioned, we employed a very stringent criteria of efficacy which was the complete relief of heartburn for a full four-hour period after the meal. Here are the results.

These are two identical studies, 005 and 006, and I'm plotting now the percent of subjects

heartburn free. In study 006 on the right, you see that there are statistically significant differences from placebo for both ten and 20 milligrams. In study 005 on the left, the percentage of subjects who experienced relief was similar to study 006, and they are numerically better than placebo, but the placebo rate here was higher. So these differences do not amount to statistically significant changes.

There are additional support of efficacy endpoints that we employed throughout our program. Each participant in this case was asked for an overall assessment of their satisfaction at the end of a four-hour period with the dosing, and we also, as I mentioned, monitored the use of back-up medication, which we think is an important parameter because it's the one way that the participant can actively describe their dissatisfaction with their dosing.

And I'm showing you here these secondary endpoints. Again, the findings in 006 were statistically significant, and in 005 only at the 20 milligram dose.

In summary, for the prevention program both ten and 20 milligrams omeprazole was effective in preventing heartburn. If approved, this will be the first over-the-counter heartburn medication that

provides all day prevention, provided taken at least one hour before a provocative meal. We think as such, it represents an important benefit to consumers who have predictable heartburn.

Now we'll turn to the treatment trials employing over 3,700 participants. Again, the same two doses of ten and 20 milligrams omeprazole were used. Now, in contrast to the 14-day prevention trials in which the people were instructed to take one tablet every morning, in these trials the subjects were instructed to take the medication when they had heartburn or, more specifically, when they would normally take their over-the-counter heartburn remedies.

Therefore, the study participants controlled their own dosing and, as such, the dosing was intermittent.

They were instructed, however, not to take more than one tablet within a 24-hour period, and back-up medication was provided.

Now, our primary endpoint to assess efficacy was a very stringent criteria of sustained complete relief, and let me explain that to you. That means that the participant had to say that within one hour of dosing, they had no heartburn. It was

completely gone, and that they had to remain at that level of complete relief for the next two full hours.

This is the first time this endpoint has ever been used in the assessment of a heartburn medication.

Now, just to reiterate, dosing was intermittent in these trials in response to heartburn symptoms. So how often were these people having heartburn?

And what I'm showing you here is the frequency of days with heartburn in the placebo patients, those people not receiving any benefit of therapy. We're looking at the frequency of days, and we found that the median number of days with heartburn was six, on average then about three times each week.

Twenty-five percent of these people had heartburn on more than -- equal to or greater than ten days. Now, if you look at days of consecutive dosing, 83 percent of these consumers had heartburn on two consecutive days, and when you start looking at longer strings of consecutive days, only about a third of them had four consecutive days of heartburn.

Now, I don't have a slide, but in relevance particular to the severity of their heartburn, before the very first episode of heartburn

about 30 percent of these people were having mild symptoms, almost 60 percent moderate, and about ten percent severe.

We'll look at the primary endpoint of sustained complete relief at the first treated episode. So this is a single day. We're looking at the percent of subjects, and as you can see, the percent of subjects on treatment who describe complete relief within one hour of dosing was not different from placebo in either study.

There are additional prospectively planned endpoints, and we can look at these. There's a slightly lower bar of sustained adequate relief, and that was measured. People had to report that there was relief of their symptoms and it was sustained, but it did not have to be complete relief.

Here we see at least a suggestion of numerical benefit, but only at 20 milligrams in study 095 did this reach statistical significance.

There were three additional single dose trials which we looked at this endpoint at a two-hour period, and these did not reach statistical significance.

These findings bring up a very important point. Is omeprazole efficacious if used to treat

heartburn?

While we didn't see any statistically significant benefits in any of those trials when we looked at one and two hours, we did have the ability to look at a three-hour endpoint because at the end of the three-hour period, we asked the question to consumers about their overall assessment, and here's the question we asked them. Overall, how would you rate the medication?

This slide shows the subjects' overall assessment of the drug, which was defined at those dosing experiences that were scored as good, very good, or excellent at the end of the three-hour period from dosing,a nd we can see efficacy in Study 095 for both does. The P values are shown, and evidence of efficacy in 092, but these did not reach statistical significance.

Back-up medicine was also assessed, and it was very similar to the results from overall assessment.

Now we're looking across the entire 14-day period, and as I mentioned, the median days of heartburn was six over 14 days. So here are the results for sustained complete relief of all treated episodes in both studies.

The Y axis gives the number of percent of episodes where there was sustained complete relief, and as you can see, significantly more people at 20 milligrams obtained sustained complete relief in both studies when assessed across the entire trial, and the response with ten milligrams was slightly less, with the P values as shown.

Now we'll look at the remaining efficacy variables across the entire 14-day period. The people reporting sustained adequate relief at both ten and 20 milligrams omeprazole was statistically significant, as you can see the P values listed.

Now, sustained adequate relief is a conventional endpoint in the assessment of over-the-counter drugs, and as such, it is the basis for the approval of the treatment of frequent heartburn.

Again, the overall assessment by consumers of their degree of satisfaction with the drug was a very consistent finding in these studies, and the use of back-up medication was also consistent with this expectation from consumers of their degree of treatment efficacy.

In summary, this clinical program consisted of well controlled trials which covered both aspects of the proposed label, prevention and

treatment of heartburn. In support of the prevention indication, both multiple dose and single dose studies demonstrated prevention of symptoms when taken in the morning or up to one hour before a provocative meal.

Omeprazole was shown to be effective in the treatment of heartburn in subjects who experienced heartburn more than once a week. We tested both ten and 20 milligrams omeprazole in our studies, and while 20 was often numerically superior to ten, ten was also effective in that it was statistically different from placebo, and very often it was quite comparable to 20.

Thank you for your attention.

And now I'd like to ask Dr. Schachtel to address us and talk about the use trials.

DR. SCHACHTEL: That you very much.

The sponsor has asked me to come here today to present the consumer use program which was conducted over the past three and a half years, and I'll go through each of these studies with you.

I have one right here. Thanks anyway. Just because I wander. That's the reason.

I will address each of the objectives and try to show you how their program as it was developing a label over the past three to four years satisfactorily addressed each of the -- of their

research.

The four objectives, of course, were do consumers understand the proposed label as it was being developed.

CHAIRMAN BRASS: We're losing the mic.

MR. SCHACHTEL: They were supposed to set this up. I'm sorry. I'll hold it then. That's better. Switch is on.

I think that Dr. Brass is right. I will stand right over here, technology being as it is.

Do consumers understand the label? And if a sufficiently comprehensible label can be developed, how do consumers use the product with that label under actual conditions of use? Do they comply with it, and do they use the product safely and effectively?

Could we go on? Thank you.

The entire program is summarized here. There are approximately 2,800 consumers in the different studies. The initial label comprehension study followed by four different consumer use studies, two of which were on the 20 milligram dose in adults; an adolescent study on 20 milligrams; and a ten milligram study in adults.

I conducted these two, the 03 and 022. So I'll tend to go into greater detail on them.

Next slide.

The label comprehension study, which was on the initial label, and there have now been two or three, in fact, developed since then, but the initial label comprehension study consisted of 504 consumers from ten geographically distributed shopping centers and with four specific cohorts in mind, namely, those who did have heartburn and those who do not.

A low literacy sample, if you will, using the then conventional REALM test, selecting those who were eighth grade or below in reading level with heartburn and without heartburn, and finally a cohort was also identified who took certain contraindicated medications or had contraindicated diseases as were then on the label.

The results, I think, are in your dossier that's been provided, but they're summarized here for each of the different communication objectives, and there was sufficient understanding of each of the communication objectives so that the sponsor felt that they could then further develop the label with the agency and put it into consumers' hands, if you will, which they did.

Next slide.

The consumer use studies consisted of

four, as I've mentioned to you. The most important feature of these, as you may recall when we designed these studies beginning 13 years ago, the purpose was to have no white coat involvement at all, and intentionally when we're at shopping centers and there are consumers there, there are no physicians present, no nurses, no pharmacists. These are lay interviewers, and the consumers identify themselves in this instance, in the two studies that I conducted. Do you get stomach problems, a purposely general term similar to the stomach remedy that one sees in drug stores or in super markets?

And if they say yes, they are given a market ready product with the label that's being tested on it and asked: is this an appropriate product for you or not?

There are no instructions to the consumers about reading it, how to read it, and certainly no questions are answered.

May I go to the next slide?

Just to give you a sense of what consumer do, and I must say that in the many actual use studies that we've conducted, this is not an atypical segregation of consumers, about 25 to 30 percent generally self-exclude, if you will, and they do this

because they may think that the product is appropriate, but they just don't want to enter a clinical trial, not atypical from the controlled clinical trials that we all conduct.

Interestingly, in this study as in others, people will tell you, "But I don't get heartburn and, therefore don't participate," and others will tell you they get the condition, but it's really not that bad, and they don't want to participate.

Fortunately, of course, some people are happy with their current medication and don't want to try anything else, and those who consider trying new medications do tell us in this study, and we've seen it repeatedly over the past 13 or so years that I've been doing these studies; there are those people who will say, "Yes, but I do want to call my doctor," and they do.

There are some who identify themselves from the label as having -- as taking contraindicated medications or having conditions that are contraindicated, and almost universally, and I've never seen this to fail, all pregnant women who read labels very carefully do self-identify, and in these studies also chose not to participate.

Then they are given a supply of the market

ready product, again, with no instructions about how to use the product and told to return in four weeks, and during that interval, they're asked to document their daily use, if they use the product or not, why they use it, if they take any other heartburn remedies, what effect the medication has on them, both beneficial and adverse.

To give you a sense of the demography or conventional demographic characteristics of the sample, these are taken from -- excuse me. These top three conventional demographic handles are taken from all of the studies, giving you a sense that, in fact, predominantly there were more women in these studies; that Caucasians were highly represented, approximately 86 percent, and I believe in your dossiers you can see the distribution for other racial/ethnic groups.

We had a wide age range, mainly because of that adolescent augmented study, average age being 44, slightly higher if you exclude the adolescents, which is not on the label as I understand it that's being applied for, and we had a purposely generous subpopulation of older persons.

If you look at the two studies we conducted where we also garnered additional demographic information, namely, education level and

occupation, 42 percent of our samples in both studies, but they were quite similar actually separately had either graduated from high school, but no higher and 63 percent were not at the professional, technical, or managerial/administrative level, a little lower, if you will, on the totem pole.

Next slide.

In terms of the clinical characteristics of these consumers, here we're looking only at, again, our two studies. When we ask them for how long have you had heartburn of any kind, a high percentage of these persons who tended to skew in age to the right, a little older, said that -- 75 percent said that they had had heartburn, in fact, for more than five years, and that they got it frequently. Sixty-two percent of them said they got heartburn during the day two or more times a week, and about half said they got heartburn at night about two times a week.

What did they do for it? Not dissimilar from other surveys and the ones that were shown earlier today, about 18 percent of them are taking or have prescriptions for heartburn therapies, PPIs, or H2 RAs, and again, as has been seen in other surveys, about 80 percent here, 78 percent are also taking, with or without the Rx drugs, are taking OTC

medications for their heartburn.

What were the results? In terms as the first objective of these studies is, what are the consumption patterns?

We looked at it in two ways. I think you have in your dossiers looking at it in terms of exclusive use. When I received that report from the sponsors, I could see immediately that fewer than half, 45 or so percent of these consumers used the product only for relief or only for prevention.

Therefore, I recommended that a convention that the agency used on several studies that I've done, namely, that we look at in terms of predominant use, namely, predominant use meaning if more than half of the time that you use the product you use it for relief. That's how we categorize these consumers. If you use it more than half of the time for prevention one hour before a meal or more than half the time for prevention for 24 hours, that's how you're categorized.

And there were about 16 percent for whom there was no way to categorize them. I might point out interestingly that if you were a preventer, more than 85 percent of the time you used it for prevention. It wasn't a squeaker, if you will, 51

percent.

And similarly, for relief it was about 83 percent of the time you used it for relief, but not exclusively, and that's why I recommended, and we're showing it here, but the exclusive use, I think, is also available if you want to look at it that way.

The next slide.

Now, the three separate indications or, rather, directions for use were also examined, and I'll show them to you separately. They are, namely, obviously not taking more than one tablet per dose.

Here, of course, there are two ways to look at it, as there are many ways to look at everything. One can look at it only on a consumer basis, and there are about 2,200 consumers, and one can also do, which is what I recommend, because it tells you each time the person took a dose, did they do it correctly or not, and of those, there were about 24,000 dosing occasions, if you will, over the four week actual use study.

Looking at it that way for each of the four studies, one can see that well above 80 percent, 90-plus percent, in fact, of the times that consumers used this Prilosec I, as it was called, they did take only one tablet per dose.

Next.

The second direction for use being how many doses did they take per day, and obviously no more than one dose per day.

On a dosing basis, there were 24,000 dosing days, i.e., days when they took at least one table. Well, above 80 percent, in this case 96-plus percent or so, of the times that they took Prilosec I they took only one dose per day.

I might add it might be of interest to you that we inquired in the 022 study, and I think this is in your booklets, of the four percent in that study who took two doses a day why they did that, and about half of them, about half of those persons had some relationship with a physician that led them to take two tablets.

And if you were to go back, if I could, to the previous slide, that 91 percent here, we know that those nine percent, about half of them also had some relationship with a physician that had led them to take more than one tablet per dose.

Now, let's go ahead, too. Finally, and importantly for this drug, this is what fascinated me, is did they comply with the dosing instruction to take for ten or fewer days, and again, we're looking at

about 2,200 consumers. Across the board it ranged from 78 to 92 percent compliance with this direction for use.

When we did our initial study 003, I decided to call the first 50 consumers that we could reach who had gone beyond ten days to talk with them, an old adage obviously for a physician, and we could see that, in fact, approximately 70 percent of those persons who used the product for more than ten days had either been taking Prilosec on prescription, had it recommended that way by their doctor, or even during the study consulted with their physician, who recommended that.

So, therefore, with those hypotheses, we incorporated that thinking prospectively into the subsequent study so that all subjects were asked the same questions at the exit interview to determine their dosing behavior, and if you go on, you can see that the 78 percent in that 022 study complied with the dosing instruction.

There were several other mechanisms, if you will, opportunities for how they interrelated with physicians, some during the study. These three people told us that their physician told them to take Prilosec that way.

These folks specifically had been given a prescription for PPI or H2Rs, mostly Prilosec, by the way, during the last year and were familiar with the product obviously so that if one were to just add up any of these, you come close to 89 to generously 94 percent, but around 89 percent of the time they were complying with the instruction to take this way unless so directed by a physician.

Next slide.

The second objective of our studies is to show what happens to consumers when they take this product under uncontrolled conditions, and in terms of safety, we saw that there were common side effects. These are the most common that were reported, and as I think you can see in the briefing document, when these side effects are recorded in double blind randomized, placebo controlled trials, they're no different from placebo.

I can also tell you that there were no serious drug related adverse events either.

Finally, and this was actually a recommendation of the agency, what is the effectiveness of this product when given as people will use it?

And so I created two different ways of

addressing effectiveness. For each dose patients were asked at the end of the day, did the medication work for your heartburn. This is exactly what clinicians do in their offices when they give a patient a new drug. They say, "Well, did it work for you or not?" the next time they see them, and it was a simple yes or no determination, very clinical.

Granted, no placebo involved. Just the way people would use it.

A very high percent through all studies both on the first dose and for all doses responded favorably. I might point out that this was true for prevention, when people used it on those occasions for prevention, and also for relief.

And interestingly, there was a discrimination by the consumers of prevention versus relief, indicating a certain sensitivity to how the drug performs. It performed 93-plus percent of the time positively for prevention and about 80 percent of the time for relief, a differentiation.

So these people are not just saying everything works and everything is fine.

The corollary to this which is clinically meaningful, I think, is that people also had the opportunity to record if they needed to take anything

else for their heartburn, and when one looks at that corollary, the use of other medications, it was three to six percent of the time only, indicating that the drug they were taking was working and they didn't have to take anything else.

Next slide.

Finally, we used the conventional rating scale that's used in clinical trials, which you've seen in the controlled clinical trials, and if one looks at the top two very good and excellent ratings for the two studies it was employed in, one can see that approximately 70 percent of the patients said it was very good or excellent, and if one includes those who said it was good, it's about 90 percent.

In summary, we saw that the label as it was being developed was well enough understood to be put into actual use circumstances, and that when that product was used, it was used according to label, and safely and effectively.

Thank you very much.

Dr. Levine is next.

DR. LEVINE: Good morning. My name is Doug Levine. I'm Chief Medical Officer of GI at AstraZeneca, and I'm pleased to prevent an overview of safety of omeprazole for OTC use.

I will show you data in support of the minimal risk of omeprazole for OTC use, including the safety of prescription use at mainly 20 and 40 milligram doses and the safety in the OTC trials at ten and 20 milligram doses.

Based on this safety review, we proposed that OTC risk potential will be well managed by dose selection, duration of treatment, and labeling instructions on seeking care.

I will speak to four main areas in this assessment: acid suppression, pharmacokinetics, general OTC safety considerations, and the documented adverse event profile of the product.

This figure shows the dose response of omeprazole on gastric acidity. The top line represents before treatment and the dips seen here and here at one and 7:00 p.m. represent food buffering effects from meals.

The second line down represents the ten milligram dose, and you can see during the daytime hours, there's acid suppression, but then at night there's return of gastric acid secretion to more physiologic levels.

The bottom two lines are the 20 and 30 milligram doses of omeprazole which demonstrate more

sustained acid suppression throughout the 24 hour period. We should keep these data in mind as we consider potential effects of acid suppression by omeprazole.

What are the potential effects of acid suppression on absorption? Achlorhydria is rare even with prescription doses. Acute effects on nutrient absorption can be demonstrated in the research setting, but depletion of nutrients is not found in prospective studies.

Absorption of anti-fungal agents can be affected, and this should be indicated in the label, but the potential for all of these effects is decreased with a ten milligram dose.

Is there rebound acid hypersecretion when omeprazole use is stopped? In most circumstances with the 20 milligram prescription dose, acid secretion normalizes within several days after stopping, but following more intensive treatment courses, such as 40 milligrams daily for eight weeks, there can be acid hyper secretion.

This phenomenon has been inconsistently observed in shorter term studies, but when it has been demonstrated, the effect is reversible.

Regarding potential symptom effects, the

OTC trials showed that symptoms were no worse than placebo during follow-up after cessation of omeprazole, and again, the potential for this effect is limited with short-term use of a ten milligram dose.

Based on animal studies, another potential effect of acid suppression is neoplastic potential. In these studies, rats treated daily with high doses during their entire lifetime showed a dose related increase in gastric ECL cell carcinoid tumors. These carcinoid tumors in rats were shown to have been caused by disruption of gastric acid homeostasis, and a weight of evidence of analysis of other data do not support a genotoxic pathogenesis.

The further neoplastic progression of ECL cells to carcinoid tumors as a result of acid suppression has been demonstrated to occur only in rats and not in humans.

Previously, the prescription of a omeprazole product had a boxed warning based on the findings of cardinoid tumors in rats, but this boxed warning was removed from the prescription label in 1995 based on long-term data in humans.

Thus, the findings in rat carcinogenicity studies have not been demonstrated to be relevant in

humans.

In patients, omeprazole 20 milligrams can cause increases in gastrin that stabilize at two weeks, but return to normal within one to two weeks after stopping. Rarely with doses of 20 or 40 milligrams gastrins go to above four times the upper limit of normal only rarely, in contrast to the eight to 15 times observed in the rats.

ECL cell hyperplasia, which is benign proliferation, can be seen, but the development of ECL cell carcinoids has not been observed in trials of omeprazole in patients lasting from one to more than 12 years.

In addition, review of clinical trial and post marketing data, there's no evidence that chronic use leads to the development of GI, epithelial neoplasia or malignancy.

To summarize the potential effects of acid suppression with omeprazole OTC use, nutrient depletion is not expected. There is a potential for malabsorption of antifungal drugs. Rebound acid hypersecretion is not likely, and GI neoplasia or malignancy is not attributable to omeprazole.

The next area is pharmacokinetics, and the potential for metabolic drug interactions. This is

based on competition between drugs for common sites of metabolism.

Omeprazole is metabolized by the cytochrome P-450 or CYP, C-Y-P system, in the liver and almost exclusively by 2C19 and 3A4. However, the affinity of omeprazole for 2C19 is the strongest so that only drugs that share this metabolic pathway have the potential for interaction.

Drug interaction studies were conducted with drugs metabolized by CYP 3A4 and these other CYP enzymes, but no potential for interaction was demonstrated. In the 2C19 studies listed here, there was a 25 percent inhibition of diazepam metabolism with a 20 milligram dose of omeprazole, but this level of competitive inhibition is not likely to be clinically significant.

The other drugs, phenytoin, R-Warfarin, and tolbutamide, are primarily metabolized by other enzymes which are not significantly affected by omeprazole.

A special population with potential for effects are so-called slow metabolizers. These are people who genetically lack CYP 2C19 metabolic function, and this occurs in 15 to 20 percent of the Asian population.

Slow metabolizers depend on the secondary metabolic pathway of omeprazole, the CYP 3A4 pathway, which is somewhat slower than 2C19, and this leads to a longer plasma half-life. The area under the concentration time curve is approximately fivefold higher in slow metabolizers, but there is no drug accumulation.

This effect is well tolerated, and it should be noted that the approved prescriptive dose for omeprazole in Japan is the same as it is in the United States.

Other special populations with potential for effects are individuals with liver or kidney impairment. Studies in the hepatically impaired show a longer plasma half-life, plasma concentrations which are approximately sevenfold higher, but again, there is no drug accumulation.

Studies in the renally impaired show that eliminate of metabolites of omeprazole is less than that in healthy subjects. So to summarized, we anticipate minimal risks with OTC use of omeprazole based on the pharmacokinetic profile. We don't expect clinically significant effects for metabolic drug interactions at CYP 2C19 or in these subpopulations.

With prescription use, dose adjustments

are not necessary for these, but because dose selection is a contributor to plasma drug levels, a decreased potential for effects is expected with a ten milligram dose.

I'll now move on to the third area involving important general OTC safety considerations, including use by children and elders, use during pregnancy, and misuse potential, including overdose abuse and chronic use.

Regarding use by children, no safety issues have emerged during clinical trials or in post marketing, although data are limited, and for that reason the proposed label now indicates the uses for adults age 18 or older.

In elders there may be reduced hepatic and renal function, but review of clinical trials and post marketing data, there's no evidence of differences in the adverse event profile in individuals over 65.

Regarding use during pregnancy, no prospective clinical trials have been carried out, but there are post marketing reports and other epidemiologic studies evaluating exposures to omeprazole, and these have been submitted to the agency in a supplemental NDA.

These data demonstrate no increased risk

of adverse pregnancy outcome.

Regarding overdose, ingestions of up to 900 milligrams of omeprazole have been reported to us with no serious outcomes. There were two deaths, but these were associated with multiple drug ingestions.

With overdose of omeprazole alone, a variety of transient symptoms have been reported, including nervous system and vasomotor effects. Data from the American Association of Poison Control Centers indicate that most reports related to omeprazole involve children under six years of age. The available data on clinical effects are consistent with the information we've received from post marketing surveillance, and the OTC label should instruct to seek medical care or recall poison control in the event of overdose.

With regard to abuse potential, there is no evidence for omeprazole abuse, for its potentiation of other drugs of abuse, or for its potentiation of effects of ethanol. Omeprazole does not affect pathways for the metabolism of ethanol, including CYP 2E1 or gastric alcohol dehydrogenase.

Another area of potential misuse is inappropriate chronic use despite label warnings. Chronic use is not likely in consumers with alarm

symptoms because omeprazole alone is not likely to improve these symptoms, but chronic use is possible in consumers who respond symptomatically, but who don't choose to seek medical advice despite label warnings.

Such consumers can be grouped into three categories. The first are those who might have a nonneoplastic upper GI condition, including reflux or dyspepsia, with or without erosions or ulcers.

The second group are those who might have upper GI malignancies.

And the third are those who might have upper GI conditions with risk of malignancy.

Coming back to the second group, which are the individuals who already have an esophageal or gastric cancer, the dominant symptoms when such tumors are sufficiently large are different from heartburn and include difficulty swallowing, nausea, vomiting, early satiety and weight loss. Often individuals with such cancers seek medical care for the first time for such symptoms when their advanced cancer is already manifest.

However, the diagnosis of cancer is unusual in the absence of alarm systems, but the presence of the alarm symptoms should prompt a visit by the consumer to a doctor.

The third potential group of chronic users would be consumers who have conditions that may increase the risk of malignancy, such as Barrett's esophagus. This condition is commonly identified in patients seeking medical care for gastroesophageal reflux disease, but progression to cancer is rare.

Unfortunately from a public health perspective it's difficult to predict who may have Barrett's esophagus and then to effectively manage the overall cancer risk.

So to summarize, we anticipate minimal risks with OTC use of omeprazole. There are no apparent safety issues in children and elders. Overdose produces nonfatal and transient effects. There is no abuse potential or potentiation of drugs of abuse.

Regarding chronic users who do not seek medical advice despite label instructions, potential deleterious outcomes that I've discussed are possible, but are likely to be unusual.

It's known that among medically diagnosed, symptomatic GERD patients omeprazole ten milligrams is less effective than the approved 20 milligram dose, which may diminish misuse potential in a subset of consumers.

The last area I'll discuss is the adverse event profile of omeprazole, and our database includes information from our worldwide clinical trials, the OTC clinical program, and post marketing spontaneously reported adverse events for which the surveillance period was ten years, covering over 380 million prescriptions. Each prescription is defined as approximately one month of treatment.

This figure depicts the most common events reported during control trials in medically diagnosed reflux disease. The most frequent events were headache, diarrhea, respiratory infection, flatulence, abdominal pain, and nausea. The frequency with omeprazole is not different from ranitidine or placebo comparators.

The profile of reported adverse events in the OTC trials is similar to these as seen on the next slide. This figure shows the most common events reported during the controlled OTC trials. The frequency of reported events was not different among the ten and 20 milligram doses of omeprazole and the placebo comparator.

In the entire OTC clinical program, there was one serious adverse event attributable to omeprazole in a 35 year old woman with multiple

allergies who developed symptoms suggesting serum sickness and angioedema. She did recover following cessation of omeprazole and treatment with antihistamines and steroids, but had a similar hypersensitivity reaction two weeks later after being treated with Sisapride (phonetic).

This tape shows total worldwide serious adverse event reports during the ten-year marketing history of omeprazole. Reading across are the two-year periods during the ten years, the numbers of total prescriptions, and then the total number of reported serious adverse events. Both prescriptions and reported events have increased during the ten year marketing history. In the bottom row is the calculated ratio of serious adverse events that have been reported to the numbers of prescriptions, and this ratio declined from almost 20 to 11.5 per million, which is a pattern that's commonly observed following the entry of a product into the market.

But what about the magnitude of these numbers? In order to get some insight on this, we looked at the reporting rates for other drugs used in the same population as shown on the next slide. Here are the calculated ratios of reported serious adverse events per million prescriptions in the first five

years of marketing of omeprazole compared to those reported with some H2 receptor antagonists.

This ratio for omeprazole is not meaningfully different and certainly not higher than the rates reported for these products, which are used in the same patient population.

One can hypothesize that this reporting rate may be characteristic of the population being treated and not causally related to particular treatments.

Here are the ten most frequently reported serious adverse events with the incidence per million prescriptions in the first five and second five years of marketing of omeprazole. These include events alluded to in the agency briefing document, such as platelet and blood cell deficits and hepatic dysfunction, but all of these are infrequent events and, again, supporting the hypothesis that this pattern may be indicative of the patient population being treated rather than the treatment per se is that the labeling for the H2 receptor antagonist reports similar kinds of events at frequencies described as few or rare and certainly events that are reported for omeprazole at these rates must be considered to be rare.

In conclusion, we anticipate minimal risk to consumers with OTC omeprazole. Its adverse event profile is similar to those of ranitidine or placebo based on our clinical trials with the prescription product and in the OTC setting.

Omeprazole has an excellent post marketing safety profile. The clinical adverse event profile is independent of dose range from ten to 40 milligrams. Any concern about risk potential for events related to asset suppression, pharmacokinetics and general consumer use would be lessened with a ten milligram dose.

Serious adverse events strictly attributable to omeprazole are reported rarely. Increased risks with long term use have not been documented, and a wide margin of safety is expected with use of omeprazole in the OTC population so that based on the safety assessment, we believe that risk potential for OTC omeprazole is best managed with these proposals: a dose of ten milligrams, which is less than the 20 to 40 milligram doses for prescription use; a treatment duration of up to ten days, which is less than the prescription recommendations of at least four weeks; and label instructions for seeking medical care.

Thank you.

Let me reintroduce Dr. Zorich who will provide a summary and close to our presentation.

DR. ZORICH: Thanks.

And I realize we're running a little over. So I appreciate your indulgence. I'll try to move along without rushing.

To conclude our portion of today's meeting, I'd like to take you through our proposed labeling and summarize our thinking in how omeprazole will contribute to the current OTC management of heartburn.

As with probably many NDAs since the time that we originally submitted the NDA and the original labeling, we've had some time to think. We've also had time to listen to the agency's questions and consult with experts in this area, including people who could give us more insight into the behavior of consumers in their treatment of over-the-counter heartburn.

And what we'd like to present to you now is our evolution of thinking and how the appropriate labeling of this product should be managed in the OTC environment.

There are three areas in the label which

I'd like to discuss. To be fair to the agency, I want to be clear that these are modifications from the original label that we submitted.

The three areas are what's the appropriate dose, what are the uses or indications, and what should be the appropriate consumer warnings. Relative to the dose, as you hear from Dr. Levine, both ten and 20 milligrams omeprazole were efficacious in the treatment and prevention of heartburn. We believe ten milligrams is the right dose because it provided benefit to consumers, and it's consistent with the precedent of H2 RA OTC products and switching at one-half the prescription dose.

As you heard from Dr. Bierer, there's now good evidence that the switching H2 RAs did not change consumer behavior. People still went to their physicians for care, and in fact, as you heard from Dr. Castell, there's good reason to believe that an increased awareness of heartburn and appropriate labeling would help bring the right consumer to the treating physician.

Now, the agency has asked that we provide clarity on who will be the consumer who will benefit from this product and how can they choose the right product that's right for them. Now, originally we had

requested an indication for the relief of heartburn. We're now proposing an indication for the treatment of heartburn because we think it better reflects the efficacy of the drug, and it will help consumers select the right OTC medication for their heartburn. So our proposal is treatment of frequent heartburn.

The data shows that consumers who choose to use omeprazole for the treatment of frequent heartburn have a meaningful benefit in the overall management of their heartburn.

We've also simplified the prevention indication from enumerating several causes of heartburn. We had listed lifestyle, stress, and exercise, and we've returned to only listing food and beverage, and the reason for that is that while almost everybody will describe a combination of factors that leads to their heartburn, still the common denominator is always food and beverage.

In addition, we've added the words to take only the days you expect heartburn to occur. We want to be clear to consumers that they shouldn't take this medication when they don't need it, and we want to also emphasize that it's not intended for continuous use.

Now, consistent with the most recent

guidelines from the American College of Gastroenterology, with input from the AGA and ASGE, we propose to strengthen our warning to provide consumers with clear directions on when to seek a physician's care and when to stop using the product or, in fact, not to use the product. So we're suggesting that we add additional alarm symptoms instructing the consumer not to use the product if they're having unexpected weight loss, trouble swallowing, chronic cough or wheezing.

In addition, it's important that consumers see their physicians if their symptoms continue or worsen, and importantly, if their symptoms are persistent and they find that they have to take the drug on a continuous basis in order to be free of symptoms. All of these are signals that the consumer would be better served under the care of a physician.

As you heard from Dr. Castell, this type of labeling could mitigate the masking of more serious conditions. We, in fact, believe that all over-the-counter heartburn medications should provide these types of warning statements so that consumers can benefit from this information.

Ten milligrams of omeprazole represents a safe and logical addition in the OTC setting. In the

spectrum of care that Dr. Castell shared with you, we've seen that lifestyle changes which are appropriate for everyone is really the basis for the first line treatment of heartburn, and acids provide temporary relief of people symptoms and with the advent of H2 receptor antagonists people for the first time could prevent heartburn when taken at least an hour before a provocative meal.

What omeprazole allows consumers to do is those consumers with predictable heartburn can manage their symptoms with greater dosing flexibility and longer duration of benefit.

Finally, very briefly I will tell you that we are committed to a consumer support program. We think that consumer education is very important. We have developed a consumer education booklet that reinforces the label messages. This booklet explains importantly what is heartburn, what lifestyle modifications can be important, and clearly, importantly, when to seek a physician for care.

We have written this booklet at the sixth grade level, and we intend to have it available in Spanish, and for those people at the lower educational levels, we'll have a video of the booklet, and for those people who have Internet access, we are

developing a comprehensive Web site.

Of course, all of our products do have an 800 number for consumer comment and any complaints.

In summary, if we go back to Dr. Bierer's outline at the beginning of our discussion, Dr. Castell did show that OTC omeprazole can be appropriate for the management of heartburn in the consumer's hands. We reviewed the data demonstrating that it's efficacious.

Dr. Schachtel demonstrated that consumers understand the product labeling and can use the product safely and effectively.

With the additions to the label as I have just outlined, we're confident the product can be appropriately labeled and consumers and health care professionals can be educated to insure safe and appropriate, effective use.

Dr. Levine showed that there is a wide margin of safety for over-the-counter use. When you consider the number of people who have taken omeprazole, the long duration of chronic use even at very high doses, there's an impressive safety platform from which we can conclude that the risks are truly minimal in the over-the-counter setting.

In conclusion, ten milligram omeprazole

can be a meaningful benefit to consumers and can be safely used in the over-the-counter environment.

Thank you for your attention.

CHAIRMAN BRASS: Thank you.

I'd like to begin the discussion with a couple of questions myself on the theme of differentiating efficacy and prevention versus efficacy in treatment or pain relief, and perhaps I could begin with slide EP27. If we could have that slide please.

This was a trial related to relief, and you suggested this secondary endpoint as evidence that consumers were deriving benefit in relieving their heartburn symptoms, but I'm curious of whether this is really a surrogate for prevention as you're assessing their experience over the entire 14-day period and whether they get sustained relief. Is that really a surrogate for prevention of episodes during that 14-day period or is it really a reflection of when they get an episode, are they getting relief from it?

DR. ZORICH: I think -- is this live? Thank you.

It's an interesting question and one that we've never really had the opportunity to address, and so you have a drug like omeprazole with its biologic

behavior, these pharmacodynamic properties, and to answer that question, I think to be honest it's both, and the reason I say that is that we -- in the 14-day prevention trials when we looked at that off study period, you can clearly see some benefit in more people being heartburn free over those three days even after off drug, but in these intermittent dosing trials, well, you have every combination of dosing you can imagine with one day, two days, three days, and then people taking period breaks, a couple of days off, and then taking the drug again. And there are as many variations in dosing as there were people on the trial.

So we've modeled the data, and we asked ourselves what is the discernable benefit to the consumer in heartburn relief, and so we just actually did a very careful study of the data that we had and said if you had been taking the drug, then what was your chance of being heartburn free the next day, and we looked at people who were taking the drug for one day, two days in a row, and then three days, and then asking that question, and then what was the chance of them being heartburn free two days later or three days later.

And what we found is that, indeed, there

is a carryover which is a discernable benefit in heartburn relief of a day. So I think that what you can say is that there is probably a combination of both further treatment and some element of prevention, and our data would say that it clearly lasts about a day, that you're still getting a benefit a day later, and beyond that you are no long appreciating the prevention benefit, but you may get further benefit from treatment.

CHAIRMAN BRASS: Do these results stratify by number of episodes at baseline or any other indicator of severity or frequency of use?

DR. ZORICH: These, what I'm showing right here do not, but we have looked, and we importantly asked ourselves the question how about these people taking it all the time versus the people taking it -- and we used the median, which was six days, and asked if you're above the median or below. Is all of the benefit coming from the high end users?

And what we found, in fact, was very comparable benefit in both of those categories. So I would say and that's why we feel confident that, in fact, it is some combination.

CHAIRMAN BRASS: Your new suggestion for proposed use includes for the prevention use only on

days heartburn is expected, and that would seem to mirror the studies such as 092 and 095; is that correct? Is that the --

DR. ZORICH: Except for prevention. This would be even before any symptoms began, but 092 and 095, it was in response to symptoms. So in 092 and 095, they already had problems.

CHAIRMAN BRASS: Okay. How about 005 and 006?

DR. ZORICH: Yes, meal induced.

CHAIRMAN BRASS: Okay. Good. I'm sorry. I picked up the wrong sheet.

And for the primary endpoint, only one of those two trials was positive.

DR. ZORICH: Yes.

CHAIRMAN BRASS: Is that correct?

DR. ZORICH: Yes.

CHAIRMAN BRASS: So what's your level of confidence that at the ten milligram dose the available data support the efficacy of that recommendation?

DR. ZORICH: Clearly, I think that as we've seen from 092 and 095 one hour. I think you're sitting right at the edge of where this drug will begin working, and in fact, in retrospect, I guess,

you know, you're probably all wondering why did you do that, one hour, but I think what we learned was unlike some of the other products, really you're just at the edge of efficacy.

And so we think that prevention during the day, as long as it's one hour or more from the inciting episode, will be effective, but clearly moving closer to the inciting episode will not be effective.

CHAIRMAN BRASS: What would be your expectation a consumer would understand from the indication "treatment of frequent heartburn"? What do you think the consumer will interpret that? And are you recommending that the label still include the one hour or the acute relief of symptoms indication in the dosing instructions?

DR. ZORICH: Actually what we've suggested is that we think that the relief of symptoms may be confusing to a consumer, and what we're hoping to target are the appropriate consumers for this product. Those would be, as you saw, it makes up about a quarter of the population of people using the product for relief.

These would be people who know that they have heartburn more than once a week.

CHAIRMAN BRASS: So to clarify, so your expectation would be that it be only used for prevention?

DR. ZORICH: It would be used for prevention in anybody. This product is like the H2 RAs in that it could be used whether you only have heartburn when you eat pumpkin pie on Thanksgiving or it could be used for treatment in those persons who had heartburn on a more frequent basis or somebody who has heartburn kind of clustered, bouts of heartburn.

CHAIRMAN BRASS: I will open it up, but again, I think that differentiation is confusing to me and may be very hard to convey on a label to a consumer as to exactly what those differences are.

DR. ZORICH: Okay.

CHAIRMAN BRASS: Dr. D'Agostino.

DR. D'AGOSTINO: Before you take that slide down, you look at the numbers and you have statistical significance, but the effects are quite small. Are you -- I mean how would you interpret that? This is a large study, a large number of subjects and so forth and 14 days. You have significance, but as I say, very small effects.

DR. ZORICH: Yes. I would say that this is not an unexpected finding in heartburn trials. In

these --

DR. D'AGOSTINO: Well, I would have expected twice as much.

DR. ZORICH: Yeah, but you know, you actually don't get twice as much. If you look across some of the other therapies, it's not uncommon to find deltas of only about ten percent. The bigger deltas --

DR. D'AGOSTINO: Those aren't ten percent.

DR. ZORICH: Well, in 095 --

DR. D'AGOSTINO: I would expect like 12, 13 percent.

DR. ZORICH: Yeah, really --

DR. D'AGOSTINO: This committee lived through all of those H2 antagonists.

DR. ZORICH: Yeah.

(Laughter.)

DR. ZORICH: With heartburn?

DR. D'AGOSTINO: With heartburn.

DR. ZORICH: Yes.

(Laughter.)

DR. D'AGOSTINO: And we weren't making money on it.

DR. ZORICH: I think Don Castell would tell you that he often doesn't make any money either,

but --

DR. D'AGOSTINO: Those may be a lot of questions, but I think I've made my point and you've made yours.

DR. ZORICH: I would like to say though that I think I would ask you to consider that these people in general had mild to moderate, and if you extend that to the population, if you look at trials in GERD patients, which are not these patients, I'm talking about people with very severe symptoms. You get much bigger deltas.

And so I think as you move to a population with lower severity, you don't see the deltas, and as you move to greater severity of symptoms, the deltas are higher, and I think that may be one of the explanations.

DR. D'AGOSTINO: Again, can I just make one comment and not a question?

DR. ZORICH: Yes.

DR. D'AGOSTINO: I think the word "treatment" takes us away from how to interpret the studies because there's prevention; there's relief; and then treatment leaves us in a very ambiguous place, and I think that's what Eric was saying.

The other question I have, and then I'll

step aside, is if I understand the studies correctly, it was an enriched population, those individuals who H2 antagonists were, in fact, effective, was one of the selection criteria. How do we interpret --

DR. ZORICH: Any OTC, not just H2s.

DR. D'AGOSTINO: Well, any OTC. So how do we interpret it? Is it that it isn't necessarily those individuals who aren't ready for a physician, but still don't have luck on other OTC medications? How do we interpret what's going to happen with those individuals?

DR. ZORICH: What the requirement was is that in the past they ere able to gain relief of symptoms with over-the-counter medications, and so what we were trying to do -- well, first of all, that's 80 percent of all heartburn folks. So that is the majority of the population.

What we were trying to do was to really make sure that we didn't have the severe patients.

DR. D'AGOSTINO: I'll step aside.

CHAIRMAN BRASS: Dr. Uden.

DR. UDEN: Yeah, I just have a more fundamental question on that slide. In your presentation, you had complete relief and that was an hour before and two hours after or three hours after.

I didn't get a good definition of what sustained adequate relief was. It was referred to in the presentation that this was what other products had done, but I couldn't find it in your material or you didn't really define what sustained adequate means.

DR. ZORICH: It means that one hour after dosing they appreciated some reduction in the level of their heartburn and that that reduction was maintained for a subsequent two complete hours.

CHAIRMAN BRASS: Dr. Elashoff.

DR. ELASHOFF: In the 24-hour prevention trials, did you record whether they used back-up medication and what were the results if you did?

DR. ZORICH: Yes, we did, and we can show those, I'm sure. Across all dosing, 171 and 183.

We did. I guess we're looking for it, but in general, back-up medication use correlated throughout all six. We collected it in every trial, and it was best correlated if you looked at the overall assessment, and I guess so it was consistent.

So if the overall assessment was numerically superior to placebo, then you were very likely to see a comparable decreased use in back-up medication.

DR. ELASHOFF: But I'm wondering about the

absolute level.

DR. ZORICH: Yeah, I'm trying to find it. We don't have it?

Well, we can get it out of our hard copy and share it with you.

CHAIRMAN BRASS: Dr. Waldum.

DR. WALDUM: I have a couple of questions concerning safety. I think that you have shown that there is a small beneficial effect of ten milligrams. I think that is shown, although it is a small one.

But I would go back to safety and that concerns the use of omeprazole in general. Dr. Castell referred to a recent review concerning safety, and that review happened to be an answer to a review that I wrote that had a completely different conclusion.

And I must say that in contrast to Dr. Dent there was no writing by the editor or any association with industry after my review -- after Dent's review it was.

Since gastric carcinoids were described in rats in their eggs, there have been a consistent question of the danger of neoplasia after PPI use. I should like to ask if our side (phonetic) killed the rats at the age of six months at that time and

examined the stomach, wouldn't they have found exactly the same findings as you find in humans today?

And if you think of the life span of rats compared with humans, I think that it is every indication that we see the same sequence in man as in rats.

I have also noticed that nobody of you have taken into consideration the role of the ECL cell in gastric carcinomas in children. We have published three or four studies describing ECL cell differentiation in gastric carcinomas, and every time you have ECL cell involved in neoplasia, the role of gastrin comes up.

And also at that AGA meeting in '96 or '97, it was described that the increased risk of gastric carcinoma in patients with Helicobacter pylori was due to the increase in serum gastrin diseased persons, and that increase in gastrin is within the level, the load level. So it is no threshold for a danger of hypergastrinemia.

And my final point will be what is the role of gastric acid. It is to destroy marker organisms, not only bacteria. Do you have any information on the destruction of viruses, prions, and so on? Do we know anything of this, that is, diseases

with long incubation time?

So I feel that risk over the contra of over pathology (phonetic) is dangerous to the public.

DR. LEVINE: Regarding the first issue that you raised, in the development program for Rx Prilosec, there were other studies done in rats in which very high doses were administered to the rats for one year, approximately half their lifetime, and in those experiments, in fact, ECL cell carcinomas were not identified. So that apparently the effect in that particular species was only seen in lifelong duration.

Regarding issues, I think that a point that you can raise regarding follow-up, we have identified the ECL cell and the stomach as the target organ in our pre-clinical studies, in our clinical studies, and in our post marketing, and what we've done is to continue to be vigilant prospectively in studies that have extended for a long period of time and have not identified any significant abnormalities in people or have received post marketing reports of the same.

DR. CASTELL: Can I have a comment?

Your serious concerns certainly are acknowledged, and I think something we've all, those

of us who have used these drugs and used them chronically have considered and worried and watched very carefully.

I think you also are aware of the fact that most of the world that practices gastrology has become increasingly comfortable with the regular use of PPIs over the last two decades, and the data such as I showed from Dr. Klinkenberg, I think, are the ones that we really relied greatly on. Her yearly endoscopies and careful screening and observations of these patients was very, very important to us.

And to date, as you also know, we have not seen anything that has given us concern. So that's basically, I think, how the evolution of our comfort level has occurred over the last two decades, but your concerns are certainly appreciated.

CHAIRMAN BRASS: Dr. Shuster.

DR. SHUSTER: I'm interested in knowing how you would differentiate the frequent episodes of heartburn from GERD and how would you educate the patients and the population as to that? That's one question.

DR. LEVINE: I respect the concern and the question that's obvious about what the definition of GERD is, and as you well appreciate, there are a

variety of criteria that physicians will use to diagnose GERD.

Heartburn is a symptom that can be seen in GERD, but I think the issue that we're trying to bring is the appropriateness for consumers who would not know what GERD is, but certainly we know can recognize heartburn, and that's really where we wanted to direct the discussions.

I recognize certainly the importance of the question intellectually, but I think perhaps as we work through the day and perhaps this afternoon we're willing to address what are the concerns about OTC use of this product in consumers who recognize their own heartburn who may or may not have GERD.

DR. SHUSTER: Could I ask also why did you exclude people who did not respond to over-the-counter medications? It seemed to me that you would strengthen your proposal if you included that group and demonstrated that you had a more potent drug here that would handle that population.

I realize that you are not making a comparative study between your drug and other over-the-counter drugs, but you did make a comparison in terms of adverse events with ranitidine, for example.

Because a lot of consideration has come

up. There are cost considerations which will be handled in the marketplace to a large extent by managed care, I guess, and ease of administration and so forth. But I would like for you to address particularly the exclusion of that group.

DR. ZORICH: We are not targeting an audience of people who have failed their current therapies. So that's one reason I think that we did not choose to study patients who had failed, and I think importantly as Dr. D'Agostino pointed out for us these drugs actually at these doses in this population are not more efficacious than other therapies out there. I think there's some degree of a halo effect for omeprazole because they are very good drugs at the prescription level and the prescription doses, which have been 20 and greater, in populations where there's been substantial use.

But in the OTC population at the doses that we studied, I did not see evidence that they were, in fact, as Dr. D'Agostino has pointed out, they're not substantially better than other therapies using comparable models.

CHAIRMAN BRASS: I just want to remind the committee that there will be plenty of time for further discussion this afternoon. So I want to focus

the discussion now on aspects of the studies and data presentation.

Dr. Cohen.

DR. COHEN. Yes, I have several questions to clarify the presentation. Firstly, data was presented on acid inhibition for the 20 and 40 milligram does, and nothing was shown for the ten milligram dose except the pH monitoring, which is not as quantitative as acid inhibition.

And the second question that perhaps you want to answer is was there any studies done on the ten milligram dose to look at healing of mucosal erosions in the esophagus over the period of recommended dosing, that is, the ten-day dosing. Does it heal the mucosa? How does it heal it? And is that a sustained response or no response?

DR. LEVINE: I can address both questions. Could I have slide 34?

I'm going to refer you to some studies from the development program where we've done another type of study. This is a dose ranging study looking at inhibition of peak acid output.

For those who are not familiar, this involves in a controlled laboratory situation administering a secreter called pentagastrin and then

measuring acid output and then the inhibition of that acid output before and after treatment.

And what you can see here is we had dose ranging from five to 40 milligrams, and I could show you table after table, but we basically believe that five milligrams was really subtherapeutic, but you could see if you focus on the percent changes certainly a dose response.

So within the development history we've looked at, you know, basal acid outputs as well as pH.

Next, if I could go to slide 46, again, this is not in the OTC setting. These are data from the Rx trials because in the OTC setting these consumers were not endoscoped to see whether or not they had esophageal erosions, but this is data actually from the Prilosec Rx label and were part of the pivotal studies for approval of omeprazole for acute healing of erosive esophagitis.

And what we demonstrated -- excuse me. These are maintenance of healing studies. My apologies. This is the best data that I have. We were able to show certainly a dose effect in maintenance of healing of erosive esophagitis where there was a dose response.

DR. ZORICH: But they had been healed.

DR. LEVINE: They had been healed before with 20 milligrams.

DR. ZORICH: Four weeks.

DR. LEVINE: Over four weeks, yes.

DR. COHEN: Well, there are no data then at the ten milligram dose for healing of established erosions, not maintenance, but healing?

DR. LEVINE: I would have to ferret those data out. I don't have those with me today. Sorry.

DR. COHEN: And the inhibition data for ten is a rather modest, if not small, acid inhibition, 20 percent.

DR. LEVINE: Yes. Clearly it's above zero. It's clearly less than 20 milligrams.

CHAIRMAN BRASS: Dr. Shapiro.

DR. SHAPIRO: There is good epidemiological evidence that the histamine antagonists do not increase the risk of gastric cancer. I'm bringing up this question because of the issue that has been raised a little earlier, rather solid evidence confirmed by the International Agency for Research on Cancer, which reviewed this about ten years ago.

Have some of the data been developed for the use of omeprazole?

DR. LEVINE: I don't believe that similar studies have been performed for omeprazole as have been with the H2s.

DR. SHAPIRO: It seems likely, based on the H2 antagonist data, that suppression of gastric acid secretion does not seem to increase the risk of gastric cancer. Would you be willing to infer that this might be the case for your product?

DR. LEVINE: Yes, absolutely.

(Laughter.)

DR. SHAPIRO: Well, I'm surprised.

CHAIRMAN BRASS: Dr. Sachs.

DR. LEVINE: Well, you know, we have to make our best medical judgments, and based on the available evidence, I would say it's true.

DR. GEORGE SACHS: It's very difficult to define an exact threshold between patients who are suffering moderate or mild versus relatively more severe. What's very clear from all the data on omeprazole, that you look to see a very nice change in the degree of acid inhibition on a 24-hour basis between ten and 20 milligrams as you showed, and this would argue very strongly that given the difficulty of quantitation of what patients should put themselves under OTC treatment, that 20 milligrams would be the

appropriate dose based on acid output studies.

Secondly, I do want to point out that the risk of gastric cancer due to Helicobacter pylori is suppression of acid secretion and ingestion of intestinal metaplasia in the fundus and has nothing to do with increased gastrin levels.

DR. LEVINE: I'd like to address the first point with slide 45, please. Again, we'll take advantage of the Rx development program for omeprazole, and again, these are data from the label.

Clearly, in a scientific setting we have a better ability to measure acid or acid inhibition, and there are a number of vagaries in either reporting or interpretation of patients' symptoms, and we perhaps lose some of the exactitude, but we do want to point out that, again, in our pivotal studies for the claim for the treatment of symptomatic GERD, again, in the Rx setting, these were patients who were endoscoped and found not to have erosive disease.

We did do dose ranging studies and found that either in all comers or in individuals who we say had confirmed GERD based on a positive pH monitoring test showing acid exposure in the esophagus, either way that you look at the patient subsets, 20 milligrams was performing better than ten milligrams.

Now, I would point out it's interesting. These studies, although they were carried out for four weeks, not ten days, they used similar criteria for rating symptom response. I think it's interesting that at least in medically established GERD over a four-week period, one can see a difference between these two doses, and yet in the OTC trials that we performed in consumers, we were not able to show really substantial difference between ten and 20 milligrams.

And whether that has to do with trial design, the nature of the heartburn or the difference between heartburn in consumers and medically diagnosed GERD patients I think is something to ponder.

CHAIRMAN BRASS: I think I'm going to stop the questioning now because of the hour and remind everybody that there will be plenty of opportunity to extend this discussion both after the FDA presentation in the context of anything they may bring up, as well as this afternoon.

We will reconvene at 10:15 promptly.

Thank you.

(Whereupon, the foregoing matter went off the record at 10:07 a.m. and went back on the record at 10:19 a.m.)

CHAIRMAN BRASS: We will now continue the morning session with the presentations by the FDA. I think Dr. Goldkind will be beginning and managing the FDA presentations.

DR. GOLDKIND: I'm Dr. Larry Goldkind, a gastroenterologist at the Food and Drug Administration, and I will be discussing the efficacy of the submission.

Dan, let's see if we can move this forward.

This is the outline of my presentation. I will briefly discuss the pharmacodynamics of omeprazole; then the review of the efficacy trials; a discussion of the current prescription usage of Prilosec for GERD and associated heartburn; briefly discuss definitions of GERD vis-a-vis heartburn along the lines of discussions earlier this morning; and then I will review the current over-the-counter template for heartburn medications and the proposed and updated proposed Prilosec I OTC label.

Next slide, please.

As was discussed earlier, the pharmacodynamic half-life of omeprazole is quite short, and this is in distinction to the pharmacodynamic properties which are, in fact, slow in

onset, developing with multiple doses over time, and following a single dose of omeprazole, only 50 percent of the maximum potential inhibition is achieved at 24 hours following that first dose.

The long acting pharmacodynamic effects are also reflected in the time to return to baseline acid secretion, which requires several days to achieve.

This slide is from a study presented by the sponsor and uses intragastric pH associated with a sham meal, which may be a more physiologic setting than the peak pentagastrin stimulated acid output that was presented earlier. On this slide you see the intragastric pH versus time following a single dose of either omeprazole ten milligrams, 20 milligrams, or famotidine ten milligrams, a currently approved, over-the-counter heartburn remedy.

Can you back up to the previous slide?

As you can see, over the five hours post dose, there is little to no change in the intragastric pH associated with the ten and 20 milligrams of omeprazole, while there is a fairly rapid rise in intragastric pH over the three hours following dose and then a fairly rapid fall off back towards baseline.