are independently controlled to produce these effects.

Regarding the genotoxicity issue, again, this is an issue -- probably omeprazole is one of the most heavily studied compounds in genotoxicity tests that exist today, other than some of the positive controls that are used in Ames tests and things.

And I'd like to ask Dr. Dave Brusick --

CHAIRMAN BRASS: I'd like to not unless you think it's absolutely critical.

DR. KINTER: I'll leave it to the committee.

CHAIRMAN BRASS: Would the FDA like to have some additional input?

DR. CHOUDARY: I'm Jaspi Choudary, supervisory pharmacologist for the Division of Gastrointestinal and Coagulation Drugs.

Dr. DeGeorge, before he left for another meeting, asked me to clarify on genotoxicity and as well as repro. toxicity and the reference that is made by Dr. George Sachs about the high doses in the carcinogenicity studies.

Let's first focus on the genotoxicity data. The genotoxicity data findings that we referred to in the Advisory Committee FDA package are referred to the sponsor studies. One is the most micronucleus

test in vivo. The second one is most bone marrow cell chromosal aberration test in vivo, and these data have been presented in 1989 Advisory Committee meeting, and this is part of the labeling.

And recent data from the sponsor's tests shows in vitro human lymphocyte chromosomal aberration tests were also positive. Now, that is the extent of the data from the sponsor.

Now, there are negative tests conducted by the sponsor. The Ames test is negative. Most lymphoma cell farbore (phonetic) mutation essay is negative. In vivo rat liver DNA damage also is negative.

So the leveling (phonetic) affects that. One doesn't cancel the other. That has to be kept in mind, and one also has to keep in mind the doses selected for the animal toxicology studies, particularly the Product II toxicology studies, carcinogenicity studies, they may seemingly be very high when you compare to the human dose, but you have to realize these doses are meant to detect certain things. They're surrogates for certain aspects of the drug effects, and those are done not at overtly toxic doses. That's what you have to keep in mind.

You also have to keep in mind what are the

exposure ratios when compared to the exposure in human, and you also have to take into account what are the dose -- how do the doses compare When putting it on surface area basis, which are more closely related to the exposure ratios?

Now, in that context, let me point out something.

CHAIRMAN BRASS: Very quickly, please.

DR. CHOUDARY: Surely. Published information does show -- published, Martelli, et al., in Toxicology, 1998, that omeprazole produces micronuclei in vitro, in in vitro tests of rat and human hepatocyte cell cultures, and in vitro human lymphoblastoid TK cell line cultures. This is published in 1998. It is more recent.

Now, the other information that is available, which Dr. Avigan also pointed out in the slide, which is not conformed later. That is, the sister (unintelligible) in human lymphocytes of volunteers who are treated with the drug, that was not conformed by anybody else. Now, those are the tests.

As far as the two toxicology studies that are concerned, if there was a dominant lethal effect, that would have been detected in the assay if there was an autopsy at the earlier part of the pregnancy,

which wasn't the case.

The things we have observed, that is the fetal loss at embryonic loss, a fetal toxicity in terms of weight loss, fetal weight, retardation of body weight, these are all detected later on during the gestation.

Now, for specifically diagnosing or detecting any preliminary indication for dominant level effects, we need to have the autopsy much earlier in gestation, say, for example, day 13 or day nine or something like that. That was not done in those cases.

The other thing is leveling indicates, clearly states, and we also clearly stated the drug did not show any anatomical teratological effects.

DR. DOUGLAS: That's correct.

CHAIRMAN BRASS: Thank you.

DR. CHOUDARY: No (unintelligible) --

CHAIRMAN BRASS: Right.

DR. CHOUDARY: But, however --

CHAIRMAN BRASS: I'm sorry. You have exactly 30 second.

DR. CHOUDARY: Sir, there is one -- one piece --

CHAIRMAN BRASS: Thirty seconds.

DR. CHOUDARY: -- of evidence that (unintelligible) recently. There is some effect on the behavioral development of the offspring of the animals treated. This is most recent.

As far as the carcinogenicity -- oh, okay. Thank you very much for the opportunity.

(Laughter.)

CHAIRMAN BRASS: Dr. Douglas, one sentence.

DR. DOUGLAS: Thank you.

What particularly raised my concern was the sister common exchange study on unexposed volunteers because that indicates that there is a form of genotoxicity in people who are exposed apparently at -- I don't know. I don't know the study -- at therapeutic doses. So it is a tie-in to the animal data, although it's not the same endpoint. Sister common exchange is not mutation. It's a reciprocal event normally, but it indicates that there is effects on the DNA.

CHAIRMAN BRASS: Thank you.

And I don't want to trivialize this issue, but from our perspective an important consideration is that it's not an OTC specific issue; that if, in fact, this drug has a major problem, it's in all

formulations, and if it's identified, if anything, it's going to be less of a concern because of the dose issues in the OTC.

So if it is a concern and these issues need to be addressed, it really applies independent of its OTC status.

Okay. So I'd like to call Question E, and without going through the entire thing again, I want to simply phrase it: are there other safety concerns that affect the acceptability of the OTC marketing of omeprazole from the list of things that we discussed and are listed below?

If the answer is yes, it means you do have safety concerns. If the answer is no, it means you do not. Yes, no, abstain.

DR. STEINBERG: Can I ask a question? Does that mean that it can be addressed in the labeling?

CHAIRMAN BRASS: Yes.

DR. STEINBERG: Or it needs to be addressed if you answer yes?

CHAIRMAN BRASS: Yes, and I think several of those points came up in the discussion. So hopefully the FDA will have captured that information.

All who would like to vote, yes, there are

safety concerns, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: All those who feel there are not safety concerns, please raise your hand.

DR. SHAPIRO: Mr. Chairman, could I raise a point of order?

CHAIRMAN BRASS: Let's finish the vote and then we'll come back to it.

(Show of hands.)

CHAIRMAN BRASS: Abstentions, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: Yes, Dr. Shapiro.

DR. SHAPIRO: Well, this has to do with my point of order. There are too many items here to answer this. I don't feel competent, for example, to judge on issues such as genotoxicity or rebound hyperacidity. So I would abstain on that.

But I do feel competent to judge on some of these items.

CHAIRMAN BRASS: And that's reflected in the discussion, but we have to have a yes/no vote.

Now, because there were so many expressions of concern --

DR. DeLAP: I was a little bit confused

about what you were voting on frankly. I think the last question just before the vote was whether you could vote yes and still think that there were concerns that could be managed in labeling, which I think might have been what some of the people were voting on.

CHAIRMAN BRASS: I'm sorry. If you think the concerns could be addressed in the labeling, you should vote no.

PARTICIPANT: Well, that's a different question.

CHAIRMAN BRASS: I apologize. I apologize. I apologize. Okay. We will go again.

A yes vote means that there are substantial safety concerns that affect the OTC marketing regardless of any labeling that would be put in place. No means that any concerns you have could be addressed in the label. I apologize. That's what I meant to say.

Okay. Here we go again. Yes, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: No, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: Abstain, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: Okay. We have to do it again. Yes, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: No, raise your hand.

(Show of hands.)

CHAIRMAN BRASS: Abstain raise your hand.

(Show of hands.)

DR. TITUS: Okay. There are eight noes, which mean -- eight noes mean?

CHAIRMAN BRASS: That there are not safety concerns.

DR. TITUS: Five yeses, which mean there are safety concerns, and one abstention.

CHAIRMAN BRASS: Okay. I propose we skip F as already discussed in the earlier discussions unless somebody has an urgent point about drug-drug interactions.

Moving on to G, and I think several of these points have already been discussed actually, in the actual use studies approximately 65 percent of the subset of subjects using the product only for the prevention of heartburn exceeded the ten consecutive

day limit for dosing recommended on the label. Note 19 to 22 percent of consumers using omeprazole for both symptoms and prevention similarly exceeded the ten consecutive day limit for dosing recommended on the label.

Do these results suggest that omeprazole will likely be used by consumers on a chronic basis for conditions other than episodic heartburn? For example, will they use it for GERD?

Is the treatment of GERD an acceptable OTC indication?

I would submit we've discussed this a great deal directly and indirectly, and I would put on the table that it is extremely likely that there will be chronic use of this product, and that the issue of whether GERD is an acceptable OTC indication, I think we have to address specifically in the context of, as I've already indicated my bias is, it's a standard of care issue, and that if a patient with GERD got symptomatic relief and continued taking this product chronically, would there be any down side in terms of their health?

Dr. Shuster?

DR. SHUSTER: One of the things that I take great pleasure in teaching house staff and

Fellows is that the patient is not always wrong, and I think in this instance the patient was right, always right because to me it's a nonissue.

You cannot prevent chronic problems by giving ten days or two weeks of treatment. The only thing you prevent is the symptoms during that ten days or two weeks that you're treating. So that's not prevention. That's treatment, and it seems to me that prevention requires long-term treatment, and that we should not criticize patients for doing that. We should applaud them. They're doing the right thing, and we would do the same thing.

And so it seems to me it should be of absolutely no concern if patients do treat themselves for longer periods than the indicated ten days or two weeks.

CHAIRMAN BRASS: Ms. Cohen.

MS. COHEN: How do you know it doesn't have something else wrong with them? I mean I go to a doctor because I don't know, and we have 50 million Americans who don't. So if I continue to treat myself, how do I know I'm not masking something more serious?

DR. SHUSTER: Well, the labeling states that they are, first of all, to see a doctor if they

are not treated successfully. If they're treating cancer, they're not going to get relief of their symptoms.

MS. COHEN: But the real world is what consumers actually do, and that's what we have to deal with.

CHAIRMAN BRASS: I think Dr. Shuster is completing his -- I mean, continue because I think your point is the critical one.

DR. SHUSTER: Well, I think that there's no way we can control what people do with antacids and with H2 receptor blockers, and so forth. People are going to do what they feel is appropriate, and I think that treating the symptoms successfully requires further treatment, and in essence that's what the doctor does, too.

MS. COHEN: You know what worries me is direct advertising to consumers because consumers all of a sudden don't think it through anymore. They see the advertising, and that's good enough for them, and they've given up thinking.

We have to get consumers to think again about what they're taking and what they're doing. We have to do better education than that.

DR. SHUSTER: We have to educate patients

as to -- and incidently, I would take issue with the term "consumers." I've always objected to this. I think it's a pernicious term. They are patients. We are not providers. We are doctors. The relationship is a doctor-patient relationship. It's not a supermarket relationship.

DR. SCHACHTEL: Just one quick remark that might help amplify this. In the 488 patients who were in the actual use study, approximately half of them, in fact, had been seeing a physician for over the past year with whom they had discussed their heartburn.

Those people who had been seeing a doctor for their heartburn, 67 percent of them went beyond ten days. On the other hand, the other half, over 240 patients who had never seen a doctor for their heartburn, the compliance was 88 percent.

So the people, in fact, who are going beyond the ten days are already under the care of a physician, and half of those have been prescribed Prilosec.

CHAIRMAN BRASS: Dr. Blewitt? Microphone.

DR. BLEWITT: I'm sorry. One has to do with current patterns of use. In other words, what's happening today in the OTC marketplace? How are people treating themselves? How much chronic

treatment is going on?

And related to that, which I really think ought to come out of this discussion, is how one defines GERD, you know, and I think what I've heard is it sounds like it depends upon whether you're a lumper or a splitter.

I've heard that GERD is a spectrum that goes from symptomatic up to significant disease, and then I've heard that there's a stigma of GERD that this is a serious disease problem.

Now, if it's a spectrum of disease, you know, symptoms or is it something that's --

CHAIRMAN BRASS: Well, here's how I've thought about it in the context of today's discussion: that what will happen is patients with chronic heartburn will undergo chronic treatment, self-medication. A subset of those will meet somebody's definition of GERD, and depending on whose definition it is, a different percentage of them will meeting it.

And my only concern is that if those patients, whatever the definition, continue to self-medicate and get symptomatic relief, are they exposing themselves to any risk or harm from not being further diagnosed?

Dr. Johnson.

DR. JOHNSON: I guess I'm getting the sense from the gastroenterologist that you don't really have concerns, and that means a lot to me because I'm not a gastroenterologist, and so I guess I'd like to make sure that the sense I'm getting is accurate and hear if there are any people that have major concerns about basically out-patient self-care of GERD.

CHAIRMAN BRASS: Dr. Waldum.

DR. WALDUM: I'm a gastroenterologist, and we, too, normally do endoscopy of all patients. We never treat patients for a long time without endoscopy.

CHAIRMAN BRASS: Could you quote data to support that practice?

DR. WALDUM: What?

CHAIRMAN BRASS: Could you quote outcomes data to support that practice?

DR. WALDUM: We feel that if you are going to use a drug for a long time, it's important for the doctor and for the patient to know what you are treating.

CHAIRMAN BRASS: Dr. Cohen.

DR. COHEN: My feeling is I don't think you're going to mask any serious underlying disease

like gastric cancer, esophageal cancer, duodenal ulcer. I just don't think it's going to happen. Although I think in the United States we try to endoscope everybody, we have not been as successful as you have been.

CHAIRMAN BRASS: Dr. Steinberg.

DR. STEINBERG: The answer is there probably are some concerns here. They're probably very small concerns. There's only a very small percentage of patients -- for instance, Barrett's would be my concern -- that we're going to miss some dysplasia on that small percentage who don't go to see a doctor, who continue to take the medicine.

But we have no data. I know what's being done in practice. What's being done is some internist or family doctor referring for endoscopies, and the gastroenterologist does it, and I, as one who does do it, see very little problems to be concerned about in the patients that I'm seeing, but there is a small concern.

CHAIRMAN BRASS: Dr. Robinson.

DR. ROBINSON: As far as I know, there's no demonstrable risk in patients self-treating for heartburn, and although we as gastroenterologists do, indeed, love to see these patients and would like to

continue our studies of an actual history of heartburn and Barrett's esophagus, as yet we can't prove that doing so is of great benefit to the patients who are so treated.

CHAIRMAN BRASS: Really, really quick, please.

DR. CASTELL: I promise it will be very quick.

Just to make everybody comfortable on the committee here, there are already many patients with GERD that are being treated over the counter with antacids and H2 receptor antagonists. So if that's a burning question, don't let it be. This is not a new change. All you're doing is talking about moving it to maybe another level, but it's already happening.

CHAIRMAN BRASS: That doesn't make it right.

Dr. Gilliam.

DR. GILLIAM: Well, I want to go -- I'm referring to page 143, and I think it's the sponsor's material, and they talk about the guidelines for the American Society for Endoscopy, and --

CHAIRMAN BRASS: An unbiased group.

(Laughter.)

DR. GILLIAM: Well, okay. But the reason

I'm bringing up is that I think when things are published like that, it becomes the standard of care, and you know, if a lawsuit is brought, people do literature searches and seeing, okay, what do the experts in that field recommend, and you know, it says here if drug therapy -- and I'm assuming that means what's currently over the counter being antacids and H2 receptor blockers and lifestyle modifications are unsuccessful, which I don't think most people follow anyway.

The endoscopy, you know, other diagnostic tests are recommended, and I'm just worried that we're going beyond what are kind of the standard of treatment.

CHAIRMAN BRASS: But, again, maybe somebody can correct me. I had interpreted that drug failure to include a pump inhibitor failure.

PARTICIPANTS: Yes.

CHAIRMAN BRASS: And so that, again, that's part of the reason why a patient over the counter who is being symptomatically relieved of symptoms would, in fact, meet those guidelines, and to me the critical warning on the label is that if symptoms persist, that that be a red flag, and we can argue whether it will be a bigger red flag than if

they didn't have to take the drug and see the red flag. That doesn't matter.

What matters to me is that that warning must be communicated very effectively.

Yes.

DR. HARI SACHS: Forgive my naivete in this regard, but let's say a patient takes this PPI over the counter. Symptoms are relieved. They stop. The symptoms recur so they start it again. Symptoms are relieved. They stop it again and symptoms recur. So they take it.

Now they've been taking it for a year. They stop it. Symptoms recur. At that point would patients be asked, "Hey, you know, you need to consult somebody"?

You know, I don't know. Okay? And from you guys from what you see, if you have a patient thing you've been following that you treat with a PPI for, say, a year, you know, they get a trial off medicine to see if symptoms recur or, you know, they stay on this indefinitely.

DR. STEINBERG: Well, we see patients referred to us that have been on all sorts of durations of therapy, and we wind up endoscoping them. There are no guidelines as to a year or six months or

anything like that, and very few of these people wind up having lesions in there that are clinically significant or worrisome, but we really don't have the data upon which to make judgments as to who should be scoped, who isn't.

I know what the guidelines are, but the guidelines I don't think are based on good data. There's impressions. There's this, that and the other, and I think as long as the labeling says that if your symptoms recur after a ten-day use you should see your physician, I would be happy with that kind of labeling.

CHAIRMAN BRASS: Quickly, please.

DR. SHUSTER: To reassure Dr. Gilliam, the guidelines that are put out by the four gastrointestinal societies are usually passed through the boards of each of the four, and it's emphasized by a preamble that is uniform for every article that comes out, and that simply states that this is a guideline and not a standard of care, and it's not to be used as such. It is based on a judgment, which in turn is based on an evaluation of the literature.

CHAIRMAN BRASS: Okay. I would like to call these questions, and does anybody object to just acclamation that it's going to be used chronically?

Okay. Then I'd like to go on to the second part of the question, and I'm going to just change it if the committee will accept it to: is the treatment of chronic heartburn, comma, including patients who may have GERD, comma, an acceptable OTC indication?

In other words, I don't think the label is going to say GERD. I think it's going to say chronic heartburn, and we need to understand that will include patients who have GERD.

Is that acceptable to everybody as a rephrasing of the question?

All those who feel that this is an acceptable OTC indication, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: All those you feel it is not an acceptable indication, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: Abstentions, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: Do those who have voted no wish to make any points that they don't feel were brought out in the discussion that are critical to their decision?

Oh, I'm sorry. What was the vote?

DR. TITUS: The vote was seven yeses, it was acceptable; six noes, not acceptable; and one abstention.

CHAIRMAN BRASS: Yes, Dr. Neill.

DR. NEILL: I'm probably being overly semantic, but I think that goes into what we've demonstrated today, which is that working for the government, Talmudic scholars, and Jesuit priests have nothing on us when we look at FDA dockets in the Federal Register.

(Laughter.)

DR. NEILL: My only concern about having GERD as a chronic maintenance or prevention of GERD as an OTC indication revolves around our ability to appropriately refer patients into physicians.

Having said that, I'm not aware that having been referred to me, since I'm the one who is able to talk a quarter of my patients into coming to you gastroenterologists, the other three-quarters continue to come to me for another few years and whine about it. I don't know that I do them any good.

Having said that, I agree that the numbers are very small, and I'm thrilled to hear a group of esteemed gastroenterologists confirm for me what I've

been doing silently and guiltily, and I'm not going to feel guilty about it anymore.

So I've abstained in order so as not to imply that this is an inappropriate indication, the caveat, again, being that the labeling for this needs to be clear.

CHAIRMAN BRASS: Again, any of the no votes want to register specific concerns that were instrumental in their decision making?

Dr. Blewitt, you had a comment?

DR. BLEWITT: I would simply add that this would seem like an appropriate -- that perhaps it's not appropriate to sort of accept that chronic use, you know, has to be maintained at its current levels. It seems to me that with appropriate labeling, but even moreover with an opportunity for a good, effective consumer education program you might be able to reduce the amount of chronic use, you know, and increase the amount of appropriate referral.

CHAIRMAN BRASS: But I think if that becomes a caveat then we play -- if that caveat becomes essential to a yes vote, then we've placed a burden of proof which I'm not sure is necessary.

DR. BLEWITT: Well, this was a post hoc statement.

CHAIRMAN BRASS: Yes, Dr. Steinberg.

DR. STEINBERG: I guess I'm a little confused. The current labeling is projected to say ten days of use. Are you suggesting that the labeling should be changed?

CHAIRMAN BRASS: We're talking generically now, not about their specific label. So that we've accepted that it's going to be used chronically. So as a general question, is that an appropriate thing to do?

The next question is: based on the results of the actual use in label comprehension studies, has the sponsor presented adequate data to substantiate that consumers will be able to use omeprazole appropriately in the OTC setting for acute symptomatic treatment, prevention up to ten days?

By, I think, our previous vote, I think the answer to that is no, that we have not seen that consumers will reliably use that, in my opinion, for a short period of time.

I think we can discuss these issues further, and again, when I say it has not been shown, it's in the context of the chronicity of use, the concern about the ten-day use, and we talked about interacting drugs and some other things. So I don't

know what other people would like to comment about conclusions from the actual use studies.

Yes, Dr. Geller.

DR. GELLER: I will say that the reported compliance is very optimistic because if you look carefully at the denominators as you go through these studies, I mean, in randomized trials, I know who I want to analyze: everyone who's randomized. But in use studies, I have this problem of disappearing denominators. You have the number who consent and meet the entry criteria, and the number who complete, and then the number who are evaluated, and these numbers decrease quite a bit.

And when compliance was reported, it was reported based on the number which the company or the people conducting these studies considered evaluable. So the numbers are very optimistic.

CHAIRMAN BRASS: Yes, Dr. Shuster.

DR. SHUSTER: Again, I'd like to point out that we are looking at noncompliance as if it were a sin, and it isn't. What I'm saying is that it's a blessing, that these are people who are doing the right thing. If they're using chronic therapy for a chronic problem, that ten days of treatment does not solve a chronic problem.

CHAIRMAN BRASS: I just want to emphasize the answer to this question is not implied to be judgmental. The question is simply put that the original intent was organized to tell consumers to use it this way. Whether that was a correct strategy or not, I think our previous discussion has shed some light on.

But we've been asked to address specifically whether or not the actual use studies addressed these factors appropriately in terms of what the intent of those actual use studies were. To the degree they identify concerns that we need not be concerned about in the future or can be modified by changes in the label, that may be good.

So I don't think this should be interpreted as a good or bad. I think it's a yes or no.

Yes, Dr. Shapiro.

DR. SHAPIRO: I feel somewhat schizoid with apologies to where we've been convinced that chronic treatment might be -- or I've been convinced -- that chronic treatment might be preferable to short-term treatment to now have to respond to this question.

CHAIRMAN BRASS: Well, we can ask him if

he would like to withdraw the question given your previous discussion, but I think we would still like to get some insight into the actual use studies and behaviors, but I will leave it to the --

DR. DeLAP: I think our biggest interest is just in knowing what you think is the appropriate use, and you know, we structured it this way kind of because this was the way the data were structured coming into us, but if you --

CHAIRMAN BRASS: I actually thought we'd get to that in I because I talks about the appropriate indication, and H was focused specifically on the actual use data, and I don't disagree that I think many of the points of the actual use study that are the most pertinent have already come out in the discussion and a judgmental or inferred judgmental discussion of it may not add very much.

DR. KATZ: I was going to say given the discussion that's gone forward so far, you can go ahead and skip H and go on to I because that will come into part of the decision making process for I.

CHAIRMAN BRASS: Thank you.

So without objection, I will so do, and I is: has the sponsor provided sufficient evidence to support the approval of omeprazole ten milligrams

and/or 20 milligrams for use in the OTC setting?

And I'll put it as an "or" so that if you think either dose has been shown you would vote yes, and I want to emphasize that this is really the critical demonstration of efficacy question. So that unless the sponsor for this particular question has shown evidence in their data presented, then your vote would be no. If you feel the sponsor has shown evidence to support the approval, then one would vote yes. So it's not an extrapolation. It's not what you think would have happened, should have happened, could have happened. Okay?

Yes, Dr. Elashoff.

DR. ELASHOFF: Is this irrespective -- let's see. Is this to refer only to efficacy issues, and that even though you might think that safety issues precluded approval?

CHAIRMAN BRASS: No.

DR. ELASHOFF: So that this is only efficacy or is this the combination of the two?

CHAIRMAN BRASS: It is the combination of the two so that it clearly says to support the approval of, and that involves both the safety and efficacy databases.

Dr. D'Agostino.

DR. D'AGOSTINO: I just want to make sure for myself that now we're going back to the six studies we looked at, and in those six studies we have some convincing evidence on the ten-day.

CHAIRMAN BRASS: That is absolutely correct. So this is based on the data that has been presented to us today, yes.

DR. D'AGOSTINO: And if we say yes and so forth, all of this discussion about GERD and chronic use and what have you, we're not saying that these studies allow us to give a blessing to chronic use since, again, within that ten days and the type of labeling that would follow from the --

CHAIRMAN BRASS: That is correct.

Yes, Ms. Cohen.

MS. COHEN: Are you going to separate out the ten milligrams from the 20 milligrams?

CHAIRMAN BRASS: I proposed not doing that. I proposed doing it as an "or." So if you thought either was, you would vote yes, and then if asked to I would separate after the initial vote.

Dr. Geller.

DR. GELLER: I'm having a little problem because the labeling is saying for no more than ten days, but we've all agreed that people are going to

not obey that, and given that they're not going to obey that, some of us believe those people should go to doctors after a certain point, which I'd rather not try to define.

So this is not a black-white issue for me here. So this overall assessment for over the counter is different from this efficacy question.

CHAIRMAN BRASS: Well, you are correct. We're talking specific -- we're going to talk about two specific populations, and we're going to separate those by the vote, and if you feel that either there are safety concerns that preclude approvability or the absence of data to support efficacy, then you would not be able to recommend approval.

DR. GELLER: I think you should say that again to make sure everybody gets the question right this time and we can vote once instead of twice.

(Laughter.)

CHAIRMAN BRASS: Okay. The vote is on -- will be on approvability. By definition approvability is based on the evidence presented to us and requires both demonstration of safety and efficacy in the OT setting for the indication that would be proposed.

DR. STEINBERG: Dr. Brass, can I comment?

CHAIRMAN BRASS: Please.

DR. STEINBERG: I think the ten milligram and 20 milligram are very different. I think the ten milligrams is the dosage, and the 20 is really very different. My feeling is you should vote just on the ten, which would be a vote separately, but it's the ten milligram that I think the discussion has revolved around.

CHAIRMAN BRASS: Okay. We will vote each indication separately for each dose. We'll do a ten milligram dose because what I'm trying, unless there's objection, what I'm trying to do is we've been presented data, and our reaction to that data will be very helpful to both the sponsor and the agency in their future deliberations and to only vote on a subset of the data, I think, minimizes our impact on the overall process, but I will accept the point, and we will separate the ten and 20 in the voting.

Yes.

DR. GELLER: I do have one question for the company. Based on the discussions here where the efficacy is clearly greater for 20, yet so are the risks, are you going for the ten? Is that what you want to do, or are you going for anything? What's going on here?

(Laughter.)

DR. LEVINE: We do not think that there's a risk issue between ten and 20. I've been trying to explain we've been talking about risk potential, given some of the theoretical issues, but we don't believe there's any risk difference between ten and 20 milligrams.

DR. GELLER: So you're going for any, anything?

DR. LEVINE: We will let you vote.

CHAIRMAN BRASS: Thank you.

Okay. Has the sponsor provided sufficient evidence to support the approval of omeprazole ten milligrams for use in the OTC setting for acute, symptomatic heartburn?

All who would like to vote yes on that question, please raise your hand.

(Show of hands.)

DR. TITUS: Higher. Thank you.

CHAIRMAN BRASS: All those who would like to vote no on that question, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: All those who would like to abstain, please raise your hand.

(No response.)

DR. TITUS: There are two yeses, 11 noes,

and zero abstentions.

CHAIRMAN BRASS: Next question: has the sponsor provided sufficient evidence to support the approval of omeprazole 20 milligrams for use in the OTC setting for acute, symptomatic heartburn?

All in favor, please vote yes at this time.

(Show of hands.)

CHAIRMAN BRASS: There were two.

All those voting no, please raise your hand.

(Show of hands.)

DR. STEINBERG: Dr. Brass, can I ask you is this vote based on the two prevention studies or the six studies?

CHAIRMAN BRASS: It is in total all the data that has been presented to us today.

Next question -- oh, I'm sorry.

DR. TITUS: There are two yeses for 20 milligrams and 11 noes.

CHAIRMAN BRASS: Next question: has the sponsor provided sufficient evidence to support the approval of omeprazole ten milligrams for use in the OTC setting for prevention of episodic or chronic heartburn?

All those --

DR. GANLEY: We need to probably --

CHAIRMAN BRASS: Separate those two?

DR. GANLEY: Yeah, and I think the other thing that's important here is the way the follow up is.

CHAIRMAN BRASS: I understand.

DR. GANLEY: If you vote yes, then you're essentially saying that there's no more information needed from them, such as an actual use study or a labeling comprehension study.

If you vote no, then you can qualify it and say we think it is acceptable for chronic therapy, for example, but you have to do these and these studies.

CHAIRMAN BRASS: Correct. Okay. So we have four votes left on Question I.

Has the sponsor provided sufficient evidence to support the approval of omeprazole ten milligrams for use in the OTC setting for prevention of episodic heartburn?

PARTICIPANT: If you're separating episodic from --

CHAIRMAN BRASS: All in favor, please raise your hand yes.

(Show of hands.)

CHAIRMAN BRASS: All opposed, please raise your hand no.

(Show of hands.)

DR. STEINBERG: Perhaps I don't understand the question. Episodic heartburn over a chronic period of time and chronic heartburn are the same.

CHAIRMAN BRASS: We are talking about based on the evidence presented to -- well, based on the evidence presented to us in totality.

DR. STEINBERG: But heartburn is an episodic issue, and I don't see how when you're talking about prevention there's a difference between prevention of episodic heartburn and prevention of chronic heartburn. They're both episodic and they're chronic.

CHAIRMAN BRASS: I think the implication was from the discussion, and again, I was happy to lump them, but I think the supposition was that a patient -- that there's an implication as to frequency and severity that would differentiate.

So, for example, prevention of episodic heartburn might be a person who has it once a month with a specifically provocative meal as opposed to the person who has three episodes a week and is taking it

on a chronic basis for that purpose.

Abstentions on that question?

(Show of hands.)

CHAIRMAN BRASS: Okay. We have to do it again because we didn't get everybody's vote.

Has the sponsor provided sufficient evidence to support the approval of omeprazole ten milligrams for prevention of episodic heartburn?

Yes, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: No, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: Abstentions, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: For ten milligrams for prevention of episodic, there are two yeses, ten noes, and one abstention.

CHAIRMAN BRASS: Has the sponsor provided sufficient evidence to support the approval of omeprazole 20 milligrams for use in the OTC setting for prevention of episodic heartburn?

Yeses, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: Noes, please raise your hand.

(Show of hands.)

PARTICIPANT: I think someone's confused. I see the gastroenterologists on the other side of the table.

CHAIRMAN BRASS: Abstentions, please raise your hand.

(Show of hands.)

DR. TITUS: There are two yeses, ten noes, and one abstention, but I don't know what we voted on.

CHAIRMAN BRASS: That was 20 milligrams for episodic.

Has the sponsor provided sufficient evidence to support the approval of omeprazole ten milligrams for prevention of chronic heartburn?

Yeses, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: Noes, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: Abstentions, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: Has the sponsor provided

sufficient evidence to support the approval of omeprazole 20 milligrams for use in the OTC setting for prevention of chronic heartburn?

All in favor, please raise your hand yes.

(Show of hands.)

CHAIRMAN BRASS: Noes, please raise your hand.

(Show of hands.)

CHAIRMAN BRASS: Abstentions, please raise your hand.

DR. TITUS: For the last two votes they were the same for ten and 20 milligrams for chronic. it was three yeses, nine noes, and one abstention.

CHAIRMAN BRASS: Now, as one of the noes, I would like to expand upon my vote and try to explain my rationale. I think that the evidence provided by the sponsor gives every assurance that this drug would have efficacy in the prevention of chronic heartburn. I am convinced of that. I tend to believe that 20 milligrams would be better than ten milligrams, and that the efficacy will be there.

I also have only very limited questions about safety, and they have to do with developing a label that can be shown to convey to consumers how to use this drug appropriately in the setting of chronic

heartburn that conveys key elements of proper use, any warnings that need to be considered, and when to see a physician; that whether or not that label ends up being congruent with the efficacy data that has already been developed or requires additional support of studies will be up to what that actual indication looks like.

My point here is that we do not have an indication, a label, an indication and studies of that label which reflect how we expect this drug to be used, nor do we have data that without knowing that it's hard to say we have efficacy data that is congruent with that labeling.

I don't know if that's clear, but that was why I ended up voting no, even though I have great confidence that this drug will be, based on the data we've been presented, be able to meet that kind of standard.

Dr. Geller.

DR. GELLER: I would like to address further the issue of the ten-day limitation. This group was unanimous in believing that would not be adhered to, and so I wonder if that should be included in the label, and if not, I think that the implication is that longer term studies are necessary.

I guess I would just like this group to discuss this to advise the company on how to proceed.

CHAIRMAN BRASS: Well, again, from my perspective if the label is for ten-day use, and that's felt to be critical for the proper use of the drug, then the sponsor has failed to meet a standard because, in fact, the drug is going to be used by more than ten days.

If the ten-day window is not an absolute window, then that needs to be better defined, communicated to a consumer and then an assessment made to see whether the existing database is adequate for that new --

DR. GELLER: Yeah, my concern is that the studies conducted don't test longer term use according to directions. So are you saying you think such studies would have to be done then?

CHAIRMAN BRASS: I'm not prejudging what a modified label would look like. So I'm not prejudging whether additional studies would need to be done.

Dr. D'Agostino.

DR. D'AGOSTINO: I have very much the same feeling in response to this question. I think that the efficacy studies for the ten days are quite good

studies and quite clear in their results.

I'm concerned as we started doing more of the talking about the chronic use of it and so forth, and it's very much what Nancy is saying, that the unfolding of actual use studies and labeling and so forth may say that you want to go beyond the ten days, and if you do, then I think you need to -- there's a point where you have to ask for more studies, and again, I think the studies are convincing, but there are so many issues left unsettled and undone that I think the discussion between the drug company and the FDA now hears our concerns and really has to be done very seriously.

CHAIRMAN BRASS: Dr. Sachs.

DR. HARI SACHS: What I think I would need to see, for example, to turn my no vote to a yes because I agree short term efficacy for prevention was shown. My concerns is the likelihood that much longer term chronic use would be done. I would want to see some of the longer term studies, and there may be data based on the prescription use which would certainly reassure me as to safety.

I think, number two, if you're putting it into the OTC market, there's going to be a lot more exposure of pregnant women who may take it for GI

symptoms, not realizing they're pregnant, and you know, that needs to be addressed a little bit. I know it has been addressed slightly, but there wasn't consensus, and I think you need to have that.

I also think there's going to be a lot of self-selection that I'm not sure was demonstrated, especially if people are going to be using it over a long term.

CHAIRMAN BRASS: Dr. Uden.

DR. UDEN: Well, first of all the acute, symptomatic heartburn, I think for both doses it was very clearly shown in the studies that how they ran them it didn't work. But in the episodic where there was mixed results and even the sponsors themselves admitted it, for the episodic they were directed to take it an hour before their challenge.

Clearly, if it's taken -- well, intuitively, if it's taken, you know, two, three or four hours before the insult, then it might work better, but that was not what was presented to us.

And so that's how the decision was made.

CHAIRMAN BRASS: Dr. Cohen.

DR. COHEN: I think that some of the panelists are trying to recreate the prescription dosage of the drug. Twenty milligram for long term

use, those data are available. That's the way we've used it for the past ten years. It's really the lower dose for short term use for the prevention of heartburn, and I can't see reinventing now the prescription dose and redoing the studies. It's clear that it works on the prescription dose 20 milligrams daily for four, eight weeks, or prolonged treatment. That was done.

Short term it works in this very limited sphere for prevention, but I think you're talking about something completely out of the context of OTC usage.

CHAIRMAN BRASS: Well, that's again why I said that it wasn't necessarily clear to me that additional efficacy would, in fact, be presented. What we have now is a complete disconnect between the efficacy data, the actual use data and the label comprehension as far as I'm concerned and what any label might look like.

Those need to be made congruent, and there are a variety of strategies that one might employ, given the expectation of efficacy and the experience with this drug that would convince people that consumers would be able to use the drug safely and with clear expectations.

I think it does no good to say we're going to fool everybody and, say, put ten days on it or ten milligrams and who in the hell cares how they actually use it. I think that if we believe that a more chronic use is appropriate and that there needs to be specific warnings, under what circumstances that's inappropriate, that needs to be demonstrably conveyed, and it may or may not require additional efficacy data to accomplish that end.

Yes, Dr. Shapiro.

DR. SHAPIRO: Mr. Chairman, just as a matter of logic, it seems to me that what has been demonstrated is that ten days of use works. We know from countless studies of prescription use that 20 milligrams of use for longer term also works.

The recommendation is ill conceived. The ten-day limit is ill conceived. If the over-the-counter use were to use it for chronic heartburn and use it as long as you like, that would make sense to me, and it seems to me logically that we already know that.

CHAIRMAN BRASS: Again, this is part of the difference between an over-the-counter consideration and a prescription. If we did not need to have some sense that a consumer would be able to

translate your and my understanding into an appropriate use in the out-patient setting, there would be no deliberation about any prescription to OTC switch because we already know they work.

And so the issue is being able to convey the key messages in an over-the-counter setting, and if there were any safety or efficacy concerns, be able to demonstrate that the label adequately addresses them.

So I don't disagree with your logic. I think it's an issue of where the bar is placed in an over-the-counter setting.

Dr. Blewitt.

DR. BLEWITT: Just for the record, these studies were carried out over 14 days.

CHAIRMAN BRASS: I appreciate the clarity. Thank you.

Yes, Dr. Ganley.

DR. GANLEY: Yeah, I just have some or one main question, and I'm getting a little mixed signals here from Dr. Cohen and Dr. Shapiro. On the one hand, Dr. Shapiro and I can understand your rationale that if people were going to take it, they should take it all the time and we can label it very easily like that, and, Dr. Cohen, I got the sense that you would

want a limitation possibly of four to eight weeks or am I wrong in understanding some of your previous comments?

DR. COHEN: My feeling is that the data that were just presented would justify approval for OTC usage at ten milligrams for short-term use, and I think most patients would use it like that.

I think if you're going for long term use, at ten milligrams you really have to present more data on what the healing rates are going to be, what the effects on the esophagus are going to be. I think that we should stick to the studies that were presented.

DR. GANLEY: Well, you had a prevention study that showed 20 milligrams was effective. Why not give 20 milligrams if there's no safety issue?

And please define what you mean by short term.

DR. COHEN: I think the short term is just the length of the study, and that's how we evaluate it today. We show that over short term you had prevention of symptoms at the lower dose, which I think is a more appropriate OTC dosage. I think that would be more embraced by the medical community, by the patient community, and that's traditional that you

go, and that's what we did with the H2s. We went to a half dosage.

It's been used. It's not been abused. It's been used appropriately, and it's had wide physician and patient acceptance, and that's what I always thought was appropriate for this drug approval: ten milligrams with the appropriate wording as presented for ten or 14 days for the prevention of heartburn.

DR. GANLEY: I think as we had thought about this internally, I think the question that came up when you connect the prevention data with the actual use data, we came to the realization that people were going to use this longer than ten days or 14 days, and our view was, well, if we're going to do that and that's an appropriate OTC indication, we ought to label it appropriately.

And I'm not sure that labeling it for 14 days as opposed to ten days really addresses the issue that we have at hand, that people are actually going to use it longer, and if they are going to use it longer, how long should they use it and should they stop and see what happens.

I mean those are the issues that we need to grapple with here, I think.

CHAIRMAN BRASS: And I think that from my perspective Dr. Cohen's logic I don't disagree with, except for the fact we know that's not what happens. A high percentage of the population won't stop at that. They use the drug for more than the intended period of time, and that the ability to be able to say whether that's correct or not or guide them in proper use.

From my perspective, I think a period of time and then a discontinuation with an instruction that it is okay to then restart the therapy or an instruction to seek medical advice or something like that, but I think, again, there has to be a match between what's actually going to happen in the OTC setting and the education of the consumer.

Dr. Robinson.

DR. ROBINSON: Perhaps I just don't read what I'm supposed to, but if I'm not mistaken, there are, of course, already OTC acid suppressing drugs on the market. I don't believe any of them are approved or have labels for long-term use. Yet we all know that all of the patients who take them take them as long as they feel they need them, and nobody has felt any need to fix that.

And so I'm not sure why you need to fix it

for this drug at this time.

CHAIRMAN BRASS: Dr. Katz.

DR. KATZ: The one difference is that the products that are out there are actually indicated for acute symptom treatment. This is not acute symptomatic relief. So there's a disconnect in one sense.

The products that people are currently taking they're taking to relieve their current symptoms of heartburn. They're taking to prevent a meal induced heartburn.

Here we're talking about, and we've been addressing the issue of chronicity of therapy so that right away you're talking about a different treatment. This acutely, as you even said earlier, would not work if someone takes it to relieve their acute heartburn symptoms.

So that we have a different drug with a different label and a different population of people who may be using it long term. That's actually what we're asking you to deal with to help us look at how would we convey the information that needs to be conveyed to a consumer so that they can understand how to use this product appropriately.

CHAIRMAN BRASS: Dr. DeLap.

DR. DeLAP: Yeah, if I can just expand a little more on that, I think one of the things that's near and dear to my heart is the notion that we should label these products so that consumers can use them to best advantage, and we shouldn't have something on the labeling of a product that we know is suboptimal or that we strongly believe may be suboptimal.

In that regard, I think one of the concerns that I had as I was listening to some of the discussion is that people are talking to their physician over the course of this research took the medicine differently than people that weren't. People that weren't talking to their physician might have been more compliant in obeying the ten-day limit, but people that actually had the advice of the health care professional were ignoring the labeling.

So that says something to me about, you know, what's the standard of care here and what should people really be doing, and then it comes back to, well, if it's the standard of care that people take these medicines longer for these kinds of situations, why can't we label it that way.

And then it comes back to, well, what else do we need to know to be able to go in that direction.

I agree, I think, with some of the

sentiment about the long history of effectiveness of this medicine for, you know, heartburn and various manifestations. So I don't have too many reservations about that, but I think we do need to have more work, and I think I'm reflecting what I've heard from the community. We need to have more work on how you label it.

CHAIRMAN BRASS: Dr. Neill.

DR. NEILL: There are also some clear implications for how many tablets go in the box, my experience being patients are going to take this. If it works, it will be a few days before they go back to their drugstore, pick up another box of 24 to take. When it doesn't work, they're going to call me and come in and ask for the different proton pump inhibitor that is not approved for OTC.

CHAIRMAN BRASS: Do you want to put your phone number on the --

DR. NEILL: No.

(Laughter.)

DR. NEILL: The implication being that because it's prescription, of course, it must work better. Otherwise why would Prilosec have gone over the counter? It can't possibly work as well.

I feel I'm the one person who voted no for

episodic and yes for chronic because I feel comfortable with the efficacy data, and while I would like to see actual use data in a 20 milligram dose or in a ten milligram dose for that indication, my level of discomfort in prevention of chronic is not so great as to feel that that requires a no vote.

CHAIRMAN BRASS: Dr. D'Agostino.

DR. D'AGOSTINO: It's been said around the table already, but I think it should be reiterated. When this committee gave its blessing to the H2 antagonist, the types of studies that were before us were relief from a meal and prevention for a meal. There was no long-term involvement involved in it. There were with the relief studies that they were spread over a couple of weeks, but it was just basically if you got an upset stomach, a heartburn, take the pill, and then we did the analysis where we actually were separating. If you took it day after day, we separated the episodes where you have to have two or three days of no drug so that we could see what was happening basically on a particular episode where there was a build-up and so forth.

These studies that we see before us are really playing on -- and the way you're describing the prescriptions -- are really playing on the build-up as

a part of the feature, and it's a new world for us, and I think that we've made the right decisions.

CHAIRMAN BRASS: Dr. Shuster.

DR. SHUSTER: I'm confused. I don't know how the FDA operates here. My impression had been that the labeling is based on and the indication is based on proven efficacy. For example, when cimetidine came out, it was approved for six weeks of treatment and very specific indications. A study in the New England Journal by Fortran showed that it was much more often used for off-label indications than for the labeled indications, appropriately so as events showed.

So my first question is: is the approval based on what we project as the appropriate use or is it based on data, evidence proven studies?

CHAIRMAN BRASS: I will try to answer that. It is based on the data that's presented in studies. In the case of OTC use, part of that database is the expectation of how consumers will actually use the product, and to the degree that there are either concerns about misleading information, use that will substantially differ from the efficacy studies that make them noncomparable, efforts have to be made to bring those two into congruence so that we

can make a judgment about the safety and efficacy in the OTC setting.

DR. SHUSTER: So what you're suggesting is that the standards for consumers is more strict than the standards for physicians, and that may have an element of veracity to it. It's probably right.

What I would wonder though is whether experts, physicians, health care professionals, physiologists, pharmacologists and so forth cannot make the decision that this is a safe drug even for use beyond the proven studies and to say that we will put it out there. I mean what you're suggesting is you shouldn't put it out there if it's going to be misused, and I think that's inappropriate.

DR. COHEN: Yeah, I would just comment that the 20 milligram dose clearly has efficacy long term. We didn't see any data that ten milligram has efficacy at 12, 16 weeks. So you're talking about long-term use, and there was no presentation of data.

CHAIRMAN BRASS: That's why I voted no.

DR. GANLEY: I think you bring up valid points, and that's why I tried to pin you down on short-term use, because generally, you know, labels say use for four to six weeks in the treatment of GERD, and then -- but that's a physician monitoring

it.

And so if you can envision here that it may say on the label for an OTC product to use it for four to six weeks and stop and don't restart it, and if your symptoms recur, you see your physician. Okay?

If you want to be very empirical about what data we have for long-term relief, but from my sense in listening to you folks today is that if you take people off this therapy and the symptoms come back, you just put them back on it. There's no empirical data in the database that suggests that's beneficial. It's based on your experience.

DR. RACZKOWSKI: Yes, I think I was thinking along somewhat similar lines to Dr. Ganley. What I'm concerned about is the potential discrepancy between the prescription labeling, which has for the treatment of GERD you need to take it for a minimum of eight weeks or so, and what we've talked about so far is the 20 milligram dose for only a 14-day course, and I'd like some advice from the committee on whether you're recommending then that if a 20 milligram dose would be approved for OTC use, would the paradigm then be for longer term, and by that I mean not just 14 days, but eight weeks, et cetera, where we do have data from the prescription use of the drug.

CHAIRMAN BRASS: Again, I think this could be handled in different ways. Again, from my perspective the indication is not GERD. It's chronic heartburn. Some patients will have GERD, and we understand that, and what I expect will happen is they will self-select out to longer therapy as long as we help guide that and have confidence that can be done safely, and that that really is kind of the critical transition.

There are some patients in this cohort who can take a 14-day course, stop, and be drug free for an extended period of time. There are others who after three days will go right back on it, and I don't think that's a bad thing either.

The challenge is how to convey that in an appropriate way to the consumer.

Yes, Dr. Steinberg.

DR. STEINBERG: First of all, I want to get back to this word "GERD." In my mind there is no difference between GERD and chronic heartburn. So I think that terminology is very confusing. I don't think it should be differentiated.

But getting back to the whole issue of the reason you voted against this being the studies are not long enough, that's one of the main things you

said.

CHAIRMAN BRASS: Again, there's a lack of congruence between the efficacy studies, the label and the actual use studies.

DR. STEINBERG: Well, the actual use we all agree is going to be long term, but long term will mean different things to different patients. So how is the sponsor to know how long term a long term study should be even if they were doing one? Should it be four weeks, eight weeks or a year? Because this drug, in effect, will be used long term for years by some people, and that's not a reasonable thing to ask.

CHAIRMAN BRASS: Well, again, there is precedent, and correct me if I'm wrong, for much of the efficacy data to come from the prescription NDA, and those studies may be used in conjunction with additional data to help support such an indication.

So, again, I don't view it as my job to explain how those standards could be met, but I'm not prejudging it the other way either. I can imagine ways to do this without additional studies, and my standard is congruence between the safety and efficacy assessment for the database, the label, and expectation of actual use, and I think there are a variety of ways to get to that endpoint.

Dr. Sachs.

DR. HARI SACHS: The other question I have, which is really additional information, is how does a patient decide whether to put themselves on an antacid and H2 blocker or a PP -- if this is OTC -- or a PPA.

You know, I think there has to be some consideration for the rather naive consumer.

CHAIRMAN BRASS: Well, I think that's the marketplace, and again, I don't think that's an issue where we, unless there's a clear health benefit distinction or risk distinction, need to guide people in doing that. I think that's a marketplace decision.

I don't -- very quickly please.

DR. ROBINSON: The only other thing I would say is that of course, I think the data that you want or need really all do exist already, and they exist in the -- and I think you're probably not looking at the data that were actually presented today totally correctly because, in fact, most patients do, in fact, take -- most of these subjects did, in fact, take their medicine according to labeling. It wasn't that most of them didn't, and the ones that didn't, you have no idea what they're going to do next, but you have no data to suggest that they'll take the

medicine for a year.

And people who have heartburn do use on demand therapy now with all of the products and will with this one as well, and if you have a bad week, you'll take it for a week, and if you don't ever have anymore trouble, you'll stop.

So the fact is putting this medicine on the market is not going to guarantee that every person that ever takes it will take it forever.

CHAIRMAN BRASS: I think I'd like to sum up briefly on a positive note because I think we're losing sight of some of the bottom line messages, and that from the perspective of NDAGC, I think we have really moved things very substantially, and that for the first time the committee has agreed that a non-acute, nonsymptomatic symptom, i.e., chronic use or prevention, may, in fact, be under appropriate circumstances an approvable OTC indication.

I think that is very significant if that can be handled right.

Additionally, I think that the concept that this product is very likely to be able to meet such a standard and there is confidence that the efficacy and safety database are appropriate for OTC if done properly is also a nontrivial, significant

conclusion.

DR. NEILL: This is not a nonsymptomatic symptom.

CHAIRMAN BRASS: Well, I'm sorry, but the patient will continue to take it while they're nonsymptomatic.

DR. NEILL: Right, but there are clear --

CHAIRMAN BRASS: So that, again, --

DR. NEILL: Unlike cholesterol, there are clearly patient identifiable symptoms that they can use to guide --

CHAIRMAN BRASS: I agree completely, but again, it is a step in a direction that allows a more chronic use during a period with an objective of prevention.

Unless there are really burning issues, I would like to adjourn the meeting and thank everybody very much for their contribution.

Oh, Dr. DeLap.

DR. DeLAP: I'd like just to add my thanks for all the hard work by the people around the table and also the sponsor and our FDA staff, of course, and I'm sure we will be having further conversations with the company, and we will probably invite a number of the Advisory Committee staff to help us in those

discussions as well.

CHAIRMAN BRASS: Thank you all.

(Whereupon, at 5:13 p.m., the meeting was concluded.)

C E R T I F I C A T E

This is to certify that the foregoing transcript in the matter of: JOINT MEETING OF THE NONPRESCRIPTION DRUGS AND GASTROINTESTINAL DRUGS ADVISORY COMMITTEES

Before: FDA / CDER

Date: OCTOBER 20, 2000

Place: GAITHERSBURG, MARYLAND

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.

Rebecca Davis