and any other kinds of suggestions that this headache is due to drug; then at some point or other, they might consider re-starting.

DR. HARPER: I would think that that isn't absolutely essential inasmuch as the passage of a few days or a week or two is not going to deleterious to the average patient with papilledema.

DR. EAGLSTEIN: Further comment or questions from the Committee, I think to any of the people who have presented. I think now or within ten minutes, we should try to start addressing the questions which we'll focus our conversation more finely.

Yes.

DR. KOEHN: Has pseudotumor cerebri, in your experience, been reported following estrogen or progesterone? I notice Cecil mentions it in his textbook that people may have been on birth control pills?

DR. CORBETT: There are a lot of alleged associations. We just recently finished a case control study of 37 patients with pseudotumor cerebri and 37 age and sex matched controls and we matched them for -- we questioned them regarding birth control pill use, of vitamin use, a great many different things, and it turns out that the incidence of birth control pill use is the same in both groups. In the group that we studied in follow-up, 22 percent of the women were on birth

control pills, which is roughly what the average birth control pill use is in this country. 9 percent of the women were pregnant and 9 percent -- 10 percent of women between 15 and 45 were expected to be pregnant at any given time so that the whole business of whether or not estrogens are really related to pseudotumors seems improbable.

DR. EAGLSTEIN: Thank you, Dr. Corbett.

Other questions from the Committee?

(No response.)

DR. EAGLSTEIN: I wanted to ask maybe Dr. Strauss and Dr. Peck, who is also here; so, perhaps I could get him. Is there -- would it be better to use lower doses and treat twice? The implication I got out of what you said was that it would be better to treat once at the highest dose, at the 1.0 mg/kg dose, but as with other drugs, it might be the total exposure. I wonder if you have any more information or can help us think through that?

DR. STRAUSS: Well, I think one of the side effects that we have not seen in the acne patients are the -- hyperostosis. I think that by going once and finishing one trial, side effects such as this are going to be less. My own personal feeling is that I would prefer to go with one course of drug and not have to retreat the drug and I think that is why we are recommending the higher dose rather than the lower dose and not having to retreat the patient.

DR. EAGLSTEIN: But that is ten times higher, 1.0 compared to 0.1?

DR. STRAUSS: That is right, because the difference in retreatment schedules was much different between 42 percent and 10 percent.

DR. EAGLSTEIN: Was everybody who required retreatment retreated or they just were defined as requiring retreatment?

DR. STRAUSS: The ones that we have there, these were actual patients that were retreated. The judgment as to whether they were retreated -- the date of the treatment was made by the individual investigator. In answer to an earlier question that Dr. Wolfe brought up, in general, those who were retreated, particularly those who were retreated, who had had lower dose of the drug were given one milligram per kilogram per day.

DR. WOLFE: For how long?

DR. STRAUSS: For up to 16 to 20 weeks, Mr. Wolfe. Some of them did go up even a little higher, particularly those who were, say, failures at the higher dose.

DR. EAGLSTEIN: So, the retreatment was with the higher dose, not with the --

DR. STRAUSS: Yes. I don't think that any of the patients who had not responded to lower dose, I think all three of us felt that if they did not respond to lower dose on the

first course, it was much more appropriate to treat them at the higher dose for many reasons.

DR. EAGLSTEIN: You gave the adverse effects, if they occurred, in over 30 percent. Wasn't the adverse effects that occurred in over 30 percent -- were there adverse effects that occurred in less than 30 percent?

DR. STRAUSS: Well, I gave just -- I mean, we have the list of adverse side effects. The point was that if they occurred in less than 30 percent, telling differences between the three dosages became increasingly difficult and that's why I just presented the data for those that occurred in over 30 percent.

DR. EAGLSTEIN: And the data also was presented in terms of the number of responders, but not the degree of response I mean, was there a degree of response even in the low dose?

DR. STRAUSS: I'm not sure I'm understanding your question.

DR. EAGLSTEIN: I am going to presume that that there -- well, I think that the data was presented, we got the number of people who responded when they were taking, say, 0.2 mg/kg?

DR. STRAUSS: Response clinically or --

DR. EAGLSTEIN: Right. Had a reduction in their lesion count, I guess, but we didn't --

DR. STRAUSS: The only graph that was measured in

these patients was the lesion counts --

DR. EAGLSTEIN: -- okay.

DR. STRAUSS: -- as far as clinical response.

DR. EAGLSTEIN: Dr. Peck, do you feel that there would be any advantage to the schedule that you associated with?

DR. PECK: Do we have an hour?

DR. EAGLSTEIN: No.

DR. PECK: Well, first of all, I, like every other dermatologist can't speak without slides. I had last week requested the opportunity to discuss this at this meeting and was told that this meeting was just going to discuss toxicity, teratogenicity, and pseudotumor and that dosing discussion would be at a subsequent meeting when the data from Dr. Strauss's study and my study could be discussed So, I do not have specific data that I can show you, you know, for the group to evaluate. There are general comments that can be made to clarify what I did. I had two clinical trials. The first one involving 40 patients with 10 patients in each. Patients with truncal acne receive a high/low dosage schedule of 2.0 mg/kg/day for either two or four weeks, followed by 0.5 for the remainder of the 16 week treatment period.

Patients with primarily facial acne had an initial dose of 1.0 mg/kg/day for two or four weeks, followed by a reduced schedule of 0.25.

MR. BOSTWICK: Excuse me, Dr. Peck, what was the truncal and the facial patients went two to four weeks on the high dose?

DR. PECK: Well, one group had for two weeks the high dose and then switched to the low dose.

MR. BOSTWICK: The truncal patients.

DR. PECK: Another group had four weeks and then --

MR. BOSTWICK: The facial patients.

DR. PECK: -- both.

MR. BOSTWICK: Both, okay. I've got you now, I think.

DR. PECK: One group had 2.0 for two weeks, followed by 0.5. Another had 2.0 for four weeks, followed by 0.5.

MR. BOSTWICK: Okay.

DR. PECK: And it was six-week trial.

MR. BOSTWICK: Okay. Thank you.

DR. PECK: That was the truncal. And in the facial, they had half of that. That was my first trial. The responses were similar in that -- again, I don't have the data, but the results were roughly equivalent to what I had shown in my initial study where I had used higher doses during the entire treatment period.

There are some specific points I would mention. In my previous studies, I found some patients did fail at 1.0 mg/kg/day and they actually did require 2.0 mg/kg/day to improve. Those were patients with truncal acne.

I found that in those patients who did have an initial flare of acne, that the initial flare was worse with 1.0 mg/kg/day than at 2.0 mk/kg/day.

Another point that I found unlike the study which Dr. Strauss presented, I think my patients were a more resistant group. He noticed that a 70 or 75 percent improvement at 0.5 mg/kg/day. In my study, it was only 50 percent at a constant dose of 0.5.

In the second study I did involving 72 patients, I chose to have one treatment, a high/low schedule of 2.0 mg/kg/day for two weeks, followed by 0.5 for 14 weeks. The control groups were a constant dose of 0.5 and they -- a group that received the high dose alone just for two weeks and then placebo afterward. And a high/low schedule worked out the best, particularly for truncal acne.

Again, additional details, I think I would require slide --

DR. EAGLSTEIN: I think the question for the Committee today would such a schedule have an advantage in avoiding these serious side effects?

DR. PECK: Okay. In my patients, the -- certainly, the severity and also the incidence of side effects were reduced when we dropped from 2.0 to 0.5 or from 1.0 to .25. In other words, if the patient had even chapped lips that were producing fissures at 2.0 mg/kg, when they dropped, the

colitis was more tolerable.

Some patients had -- at the higher dose which disappeared at the lower dose.

Taken as a group, you may not see those difference in the sense that -- if you're combining -- if you have a patient with, let's say, colitis and you include mild, moderate and severe in your -- you don't separate them out statistically then you may not pick up the differences of dropping the dose. I think the question could be analized, you know, by the data that Roche has in terms of scoring of mild, moderate and severe dropped in those patients where we did drop the dose. We'd just have to analyze the data to give you a more specific answer.

DR. HASERICK: Dr. Peck, indulge me a little. I heard of your patent several months ago and in the words of my little grandaughter, "it blew my mind." I never heard of a doctor patenting a dose schedule. There must have been some good reason for that. Do you want to explain it?

DR. PECK: The --

DR. TABOR: Let me come to your rescue for a minute. I think that you ought to realize that this is probably -- unless I'm incorrect -- not just an NIH policy, it's government-wide and it is conducted by the Commerce Department through the National Technical Information Service to patent any invention either for use or for a new substance in order to

encourage development of government inventions.

DR. PECK: I think there was even some suggestion that government, at least NIH, would be more self-supporting with that system, but, in general --

DR. HASERICK: In other words, you got no personal gain out of it? It was strictly to NIH?

DR. PECK: -- there is no gain at this point in the sense that, as you heard from Dr. Wolfe, there was $50,000 fee paid from Roche to the government. In terms of that 3 percent that was mentioned afterwards, that would depend on the Committee approving it and apparently if -- which was something new to me about 3 percent of the increase over the previous level of sales, and I don't see any reason to expect any increase level of sales after, at this point, so, I would be receiving 3 percent of nothing. The point is that in using high/low dosage schedule was unique in a sense that the dose can be dropped at the second week at which point some patients are actually worse than they were at pretreatment, or they -- certainly there is usually no benefit at the two-week point in the patients that I've seen. So, with an unexpected finding that you could drop the dose at that point and then expect improvement later on.

DR. CHANCO-TURNER: I have a question to ask both Dr. Strauss and Dr. Peck. In the two studies that were presented done by either -- both of you, the graph showing the

effects, the end effects 12 weeks after treatment using .1 and 1.0 mg/kg seems to pretty close at the end of the 12 week follow-up period, but in the other study that Dr. Peck did, there was a difference, a very marked difference at 18 to 24 months between the results from .1 and 1.0 mk/kg; so, what you really are looking for is since Accutane is being touted as a cure for acne, we really are looking for that effect that would be persistent not just for 12 weeks after treatment, but forever. So, I think when we are discussing dosing, we have to take this into consideration. I don't think Dr. Strauss' study has been going on long enough to be able to address that question of 18 and 24 month follow-up.

DR. STRAUSS: In terms of the study, as you justly noted, at 12 week post-therapy, there was relatively no difference between the three doses. When we say retreatment, that questionnaire that we sent out and that data on whether they needed retreatment was based upon observation of these patients for as long as 18 to 24 months. So, it was an 18 to 24-month follow-up on these patients.

DR. EAGLSTEIN: Dr. Evans?

DR. EVANS: I'd like to make a comment on the dosing regimens. You may be aware that much of this material, while it has been accumulated, has not been presented in formal fashion to the Agency. Once it is, meaning the data from Dr. Peck, and also the data from the Roche Company, which was

just revealed to you, we will be in a better position to digest it and bring it before the Committee. We didn't feel that this was a point to evaluate different dosage regimens because we simply didn't have the material at hand to digest and put before you.

DR. EAGLSTEIN: Are there are other questions from the Committee, or do you want to go on?

DR. GOLDNER: Would someone, maybe Dr. Strauss comment on the recent report in JAMA from the California group of Hypercalcemia. Is that an isolated report? Is this something that you have seen in others?

DR. STRAUSS: I haven't personally seen any.

DR. GOLDNER: Are you familiar with that report?

DR. STRAUSS: Yes. I don't know whether the company has any data of that nature in their files.

DR. HASERICK: Before Dr. Strauss and Dr. Peck get away, I'd like to propose a suggestion to them and let them tear it to bits or approve it, or whatever.

When we give out methotrexate, we give it out in our offices, don't we? We have to do this and we control it by laboratory studies. Why not give, as I do with my pregnant possible young ladies, I give them their Accutane on the third day of a menstrual period, and 28 days later, I see them. And if they have menstruated -- and I only give this, by the way, to the girls who have regular period, the rest of them

go on the pill. So, the girls who are regular, they get it every 28 days. Why don't we just put some kind of a control of this thing so that doctors have to give it out and see them every 28 days and make sure that they have mestruated before before they get another monthly supply?

DR. STRAUSS: Dr. Haserick, I'm not sure that's totally practical because there are drug laws that vary from state to state. I cannot in my pharmacy -- in my department, give out oral medication.

DR. HASERICK: So, what do you think of the idea of giving it on a 28-day restriction. She comes in three days after her menstrual period has started and you give her another 28 days. That's a monthly thing.

DR. STRAUSS: I'm not sure that is completely practical, whether they can get in at that time, the extra cost involved. It is theoretically a good suggestion, but I think in terms of practicality, I'm not sure it is really practical.

DR. HASERICK: I'm trying to prevent birth defects.

DR. EAGLSTEIN: Other questions?

Dr. Koehn?

DR. KOEHN: I wanted to ask either of you, out of curiosity, after you have a recalcitrant person to Accutane to one course of it, have you used control people while putting others on and the control people being people who don't have

anything, or they get tetracycline or minicycline, or one of the standard antiobiotics. In other words, do they -- might they again be controlled by antibiotics?

DR. STRAUSS: I don't think there are any control studies of that nature. I would tell you that that my own personal decision as to whether to put them back on Accutane, they have to have a severe -- continued severity of their acne.

If I get patients who have a mild recurrence, I then would try alternate forms of therapy, antibiotics, et cetera, et cetera, but in terms of a controlled study, particularly where we have treated these patients with the lower dosage, if they have not responded to the smaller dosages, I think we are morally responsible for giving them adequate therapy. Because once again, regardless of what Dr. Peck said that he didn't think our cases were as severe as his, I can assure you if I had the pictures here, and as you said, you need pictures as a dermatologist, I could show you patients that were very, very severe. So, I don't think -- I think we've had a moral obligation where a patient has undergone a dose which has not caused him to respond, to go to a more adequate dose.

DR. KENNEY: John, I would like to ask from your own experience, and what we have heard here about the possible synergistic effect of tetracycline with the Accutane, and so on, have you been keeping your patients on antibiotics along with

Accutane? I don't mean your studies, strictly study patients, but your clinical patients in your own practice?

DR. STRAUSS: My instruction to my staff members and my residents at the present moment is that if the patients are on tetracycline or monicycline, or other tetracycline derivatives that they get them off as quick as possible. And if it's required that they continue other antibiotics that we make a switch to Erothromycin, and as far as I know from talking to Dr. Corbett, there have been no cases of pseudotumor cerebri reported from Erothromycin.

DR. EAGLSTEIN: Professor Bilstad has several questions.

PROF. BILSTAD: I would like to ask Dr. Strauss, what were the total number of patients who were entered into your study, you mentioned that there were 141 evaluable patients, how many were entered and what were the reasons why patients were considered not evaluable?

DR. STRAUSS: There were 150 patients entered into the study. It was designed to have 50 per cell. Those patients that were excluded were ones in which there were missing laboratory or clinical values, and, therefore, were not considered to be appropriate to include in the full statistical analysis.

PROF. BILSTAD: Did any of the patients have to stop therapy because of side effects?

DR. STRAUSS: As far as I know none of them had to.

DR. EAGLSTEIN: I think we really -- there is always a tendency to talk about dosing and where there's data, to talk about a data. A lot, however, of the questions that we have to come to grips with deal with adjustments to labeling and other such considerations. So, why don't we take a 10-minute break and come back and work on these questions.

(Whereupon, at 11:40, the meeting was recessed, to reconvene at 11:50.)

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AFTER RECESS

(11:55 a.m.)

DR. EAGLSTEIN: If we can come to order, again. Dr. Kenney, I am sure, will be along. His cab probably got lost again.

I know that there are many, many areas -- many questions people who have been participating this morning still would like to bring or ask, and information they would like to have come out, and I think it can come out in the course of dealing with the questions addressed to the Committee, and I would like to take them up in order to try to refine our conversation a bit.

At the beginning of the booklet that the Committee members and others have, the first one is the contraindications, warnings and precaution section of the Accutane package insert. And I would like to point out this is the physician package insert. And the labels we are talking about will be under F. So, we are right now -- although the petition addressed changes in our mandated patient package insert, there were also questions about the extent or the existing physicians' package insert that has been revised once.

So, this is the contraindications, warnings and precaution section of the Accutane package insert have been revised to include new information on the teratogenic effects of Accutane, including bold face type. Is further revision

in the label concerning these teratogenic effects necessary?

So, this is a question of the teratogenic effects. There have been changes in the label, as you can see in insert F, including bold face. The changes are contraindications, which is on page 2 and there are also changes on the warning section, which is also on page 2 in the middle and in the precaution section, which is on page 3 of the amended insert.

So, the question: should more be done? And I think the FDA has taken a position before our meeting on the latest communication that you received this morning, and they have some suggestions as to what should be said in the warning section. Do you have that memorandum?

See, there are really three responses, as I said at the first, and then the petitioner has some suggestions as to what should be done, and that is under tab E.

And as regards teratogenicity, the petitioner says it should be placed in a box along with the additional information that women of child bearing potential should not be given Accutane until pregnancy is excluded by means of a pregnancy test, which I think is also a part of the FDA's position, although they don't call for it to be in a box.

Was that stated correctly?

DR. EVANS: Yes.

DR. EAGLSTEIN: So, does everybody feel comfortable that they understand what is happening?

DR. TABOR: In terms of the FDA position, even though it is typed in capitals, we meant for the format either capitals or bold type or box to be discussed here with the Committee.

DR. EAGLSTEIN: Okay. So, the box would be acceptable to the FDA as would bold type.

The company has chosen bold type, but does not have the requirement for a pregnancy test, which the petitioner asked for and the FDA asked for.

So, who wants to start off the discussion of this question.

The question is: is further label revision necessary regard teratogenicity? And I think if the answer is, yes, we can go a bit further and say what we think the labeling should be, or what changes should be suggested.

Do you want to vote on this?

DR. GOLDNER: I think we should start some discussion. I believe that additional warning is necessary. I think we do have to funnel in on pregnancy tests as to whether or not that is mandatory. Are you going to put that in the package insert. That's the significant point of that question to me. I don't think there's any question, but that we should make our warning as strong as possible. That's where we need discussion.

DR. EAGLSTEIN: All right. So, you favor the idea of a required pregnancy test?

DR. GOLDNER: No, no. Wait a minute now. I didn't say that. I did not say that.

DR. EAGLSTEIN: Okay.

DR. GOLDNER: I said that requires discussion as to whether or not it belongs in that warning.

DR. EAGLSTEIN: All right.

DR. RASMUSSEN: I agree with Ron's position. I think that the strongest possible warning should be put in there and I think the discussion should be more focused on whether you want to do a pregnancy test primarily because -- I'm not sure that that's absolutely necessary any more. My problem is with people who develop pregnancy while they are on the medication and it would probably make you have some people get substantially bent out of shape, particularly the 15, 16 and 17 year old girl who is a virgin, and then you have to send her for a pregnancy test, and they find that you don't trust them.

Now, that shouldn't be a major stumbling block, but I think it is worth considering.

DR. POMERANZ: I'd like to say I support your position that it should be as strong as possible. I feel very strongly that there should be a pregnancy test absolutely. And a 16 year old girl who is bent out of shape -- 16 year old girls these days are pretty much hep --

(Laughter.)

DR. POMERANZ: -- and I don't think they are going to be bent out. They will be pleased if the test is negative and then we can start their Accutane.

(Laughter.)

DR. POMERANZ: And it will reaffirm their virginity to their parents.

DR. HASERICK: I disagree strongly with my fine associate, Dr. Pomeranz. I don't think we should include that at all. I think that we might suggest that it be done, but I certainly don't think we ought to insist that it be done.

DR. EAGLSTEIN: Do you want to add additional reasons that you don't want to do it?

DR. HASERICK: Well, I agree with Dr. Rasmussen on it. Our girls are a little more -- not as sophisticated as those in Cleveland.

(Laughter.)

DR. HASERICK: It really is insulting. Everybody gets the word that they've had a pregnancy test, believe me, in our area.

DR. TABOR: Why should anyone get the word that someone has had a pregnancy test?

DR. HASERICK: Laboratory girls talk.

DR. TABOR: Do it in your office. You can do a slide test in your office.

DR. HASERICK: Under an assumed name?

DR. TABOR: Your records can be kept confidential

surely.

DR. POMERANZ: Well, I recognize that that's probably a problem in a small town. I actually live in a small town outside of Cleveland; so, I can appreciate that. But I think that is small potatoes in comparison to the possibility of a malformed fetus. I think that those are the kind of things -- I think it brings to the patient's attention, the physician's attention that this is a serious business and that there can be a malformation. If they happen to get pregnant, the baby will be malformed and it focuses -- it gets their attention more than anything else will do.

DR. EAGLSTEIN: Is it less pe pejorative because it would be mandated by the law?

DR. HASERICK: Yes. That is what I object to. I think if you said, it is suggested that a pregnancy test be performed no earlier than two weeks before the onset.

DR. POMERANZ: How about strongly suggested?

DR. HASERICK: All right, strongly. I'd even go along with that.

DR. EAGLSTEIN: I was saying, wouldn't you be off the hook if you had no choice, as it were? It's not that you suspect that this person is or isn't pregnant. That is just part of what has to be done. It is not a matter of your having a choice.

DR. POMERANZ: In a way it takes the heat off the

physician.

DR. HASERICK: Since I only give it on the third day of menstrual period --

(Laughter.)

DR. POMERANZ: Well, I like your idea. I wish that it would be practical.

DR. HASERICK: It is practical. The usual cycle is 28 days and that's four weeks away. Thursday to Thursday, that's when I see the patients.

DR. GOLDNER: If they can come in?

DR. HASERICK: They don't get their medicine if they don't menstruate.

DR. CHANCO-TURNER: I think I agree with Dr. Pomeranz. I'll go down on that side because for the very same reasons, specifically that it will show the patients how important it is. I don't have an 16 year girls on Accutane, and if I did, I probably would have the mother around before starting the patient and that would also reinforce to everybody conerned that this is a serious business. I am very conservative about using Accutane; so, it doesn't bother me at all. I think it should be really.

DR. EAGLSTEIN: Dr. Bilstad, you had wanted to get some further information as to exactly how many cases do we know of?

DR. BILSTAD: My question is to the Hoffman-La Roche

staff. How many pregnancies are they aware of currently, or have they been aware of prospectively, and what is the outcome in all of those pregnancies that are known and in which there was drug exposure during the first trimester?

DR. EAGLSTEIN: Is Dr. Yard here? Who will reply? Who would like to reply?

DR. YARD: Dr. Eaglstein, I would like to ask Dr. John Pepper to answer that question.

DR. EAGLSTEIN: Okay. The question is: how many people have been exposed while pregnant? Is that the question? That are known?

DR. BILSTAD: It is how many are known ahead of time, not retrospectively, but they are known to be pregnant. They are known to have been exposed to the drug during the first trimester, and the question is: how many of those is the company aware of? And what is the outcome in those in which an outcome is known?

DR. PEPPER: Prospectively, we have been aware of five pregnancies prospectively. Of those five, four had normal babies; however, the Accutane exposure in those four was extremely limited and not at an apparently critical time. At the moment, in addition, we have 20 ongoing prospective pregnancies where the patients became pregnant either while on Accutane or alternatively within one month of discontinuing Accutane. In other words, we are following up on those young

ladies who have become pregnant within a month of discontinuing Accutane therapy.

DR. BILSTAD: You haven't mentioned any spontaneous abortions?

DR. PEPPER: Spontaneous abortions, we have had a total of six. We have had two missed abortions. They were -- ended up having a D&C. There was one threatened abortion, which also ended up having a D&C.

DR. HASERICK: Isn't this really another question though. Why don't we decide about the pregnancy test. We can go to abortion later if we need to once the lady is pregnant. So, let's settle this issue.

DR. EAGLSTEIN: I thought it might give some further feeling for the magnitude.

Do you have further questions here?

DR. BILSTAD: Not on this issue.

DR. HASERICK: I think I am just against compulsion in general.

DR. EAGLSTEIN: All right.

DR. HASERICK: It plays against my grain.

DR. POMERANZ: I am, too, I really am, and I'm not happy about it, but I don't see anh other way of really bringing to the patient's attention that, you know, because 20 pregnancies that is terrible. I mean, that's 20 complete failures of communication somewhere along the time. To me, it

is just terrible.

DR. RASMUSSEN: Well, it doesn't have to mean that there are 20 failures of communication, although it certainly could be. I think what we have to not forget is that no form of contraception is 100 percent effective except abstinence, which somebody has already previously mentioned, and that is one of the things that I think we ought to consider whether or not down the line, we tell people who are on contraceptives that this drug is used on a total of 300,000 patients. Even given the effectiveness rate of all birth control pills, 98.9 or 99 percent, you are still going to have half or 1 percent of those people who get pregnant, and even with the pregnancy test, you are still going to have to deal with this type of an issue.

DR. POMERANZ: But the fact is that there may be patients who will elect to abstain for the 20 weeks that they have to be on the drug, or whatever the period of time is.

DR. RASMUSSEN: Well, I have found --

DR. POMERANZ: Give them that opportunity and really nail it down. Lay it out in the strongest possible terms. Every child that is born that is going to be abnormal is going to cost the government or somebody a million dollars until they eventually die. And it is going to cost the company a lot of money too if some of those go to court because there is a failure, and I would think that everything that could

be done to prevent a pregnancy should be done even though I'm not happy about compulsion either.

DR. HASERICK: How many of those 20 children had a pregnancy test before they were put on Accutane? Do we have any idea about that? My point is, your pregnancy test, you know, is great. It would be lovely to do that on all these things, but I'm not so sure it would prevent pregnancy.

DR. TABOR: It is not designed --

DR. HASERICK: You make a good point. We have to educate them, and maybe this is leverage enough to do it, but I like to know, give it on the third day of mestrual period.

DR. TABOR: -- I think it is not designed to prevent pregnancy, and even though it may have the effect of bringing the message home, it is not designed for that either. It is desgined to determine whether the patient is pregnant at the time you start the therapy with Accutane and it will do that. It will do it better than asking the question, are you pregnant?

DR. KENNEY: How about the menstrual period?

DR. RASMUSSEN: And it isn't 100 percent accurate.

DR. TABOR: No, it isn't 100 percent accurate, that's true. I think there is a certain amount of lack of data about exactly why these 20 patients became pregnant. Was it a failure of communication, or is the drug perhaps interferring some way with some method of contraception? Is anything known

about that, Dr. Pepper?

DR. PEPPER: Nothing official that I am aware of. I understand that there was a study performed in Britain attempting to determine whether there was interference with the BCPs, but I have not seen the data on that.

DR. TABOR: But in these 20 patients whom you have followed up to whatever extent possible, is anything known about whether these 20 women were on birth control measures that failed, or was it a failure of communication?

DR. PEPPER: I think in a lot of cases, it was a decision by the young lady not to use birth control measures

DR. RASMUSSEN: Do you know how many of the patients were pregnant at the time the Accutane was started, or how many of them subsequently became pregnant during the course of Accutane treatment?

DR. PEPPER: I couldn't give you the exact numbers by memory, but a substantial number. I would say about 25 percent were pregnant just at about the time they started the Accutane.

DR. POMERANZ: See, I see that as a failure of communication. If the patient got pregnant while she was on the drug, somebody didn't point out to her how serious this was.

The other point that I would like to make is that I don't see why you can't incorporate your idea into the package insert as well as to an alternative approach which

would be to give the drug every 28 days just after, starting after the menstrual period. I mean, that would be a short sentence and probably, you know, I think it is a good idea and belongs in the insert as well.

DR. HASERICK: Why don't you write that sentence.

DR. GOLDNER: In order to do that -- in order to incorporate that, you still have to take a pregnancy test -- a pregnancy test should be performed to strongly suggest it, or put some other word in there.

DR. POMERANZ: I think both approaches could be in there.

DR. GOLDNER: Well, I think you are manding -- once you say, "should be," you are mandating pregnancy tests. The objection that I have to it is really that mandate rather than the fact that I want to know whether my patient is pregnant. Of course, I do, and I can use whatever clinical judgment I have, whether it's the menstrual period; whether it is my relationship with that patient and knowing how accurate her history will be, or what else, but I object to the mandate, and I object to --

DR. POMERANZ: How about strongly recommend?

DR. GOLDNER: -- I don't object to strongly recommend. I object to should be performed.

DR. POMERANZ: Well, I think strongly recommended is almost should be performed.

DR. GOLDNER: Almost, but not quite.

DR. RASMUSSEN: Well, you could pharse it by saying that if there is any concern that they patient may be pregnant that that would be a good avenue to go. And that would still allow you to be confident in your own mind if the patient is not pregnant, if for some reason, patient reliability, whatever you want to call it, you can still do that and that would be suggested in the recommendation.

DR. HASERICK: You could just add, if there is some question of pregnancy.

DR. RASMUSSEN: Or if the patient is absolutely not sure.

DR. HASERICK: Then you could ask for the test to be performed not earlier than two weeks before the onset of Accutane therapy?

DR. POMERANZ: I think that dilutes it. I think it is stronger to say that the pregnancy test is strongly recommended, and that in a way, too, also -- that's virtually recommended, and that's almost mandatory. From a medical legal sense in some ways it would be mandatory, and it might accomplish the same thing without making it absolutely mandatory, but I think it should be as close to mandatory as it can possibly make it.

DR. KOEHN: It does already say that women of child bearing potential should not be given Accutane until pregnany is excluded.

DR. HASERICK: Where does that say that?

DR. EAGLSTEIN: It's on page 2.

That is the revised.

DR. GOLDSMITH: This insert is now presently being used. It is the one called revised. Already it says that blood lipids should be obtained. There is a should be in the product insert already. This is not -- that's what I wanted to say.

DR. EAGLSTEIN: Okay.

DR. TABOR: I think part of the problem revolves around how you are going to exclude pregnancy, and I think this is probably -- teratogenicity being one of the more important things we are dealing with today, one suggestion has been require or request a pregnancy test. Another suggestion has been to give it on the third day of the menstrual period and both of those, I think, most people on a scientific basis would probably find acceptable if they were practical. I think that the problem arises when you rely on history or when you rely on the patient coming in to the office with her mother, or there being other social constraints that prevent you from properly determining that there is no pregnancy.

I think in those situations, most people would, if they were being frank, would agree it is not reliable -- not a reliable way to exclude pregnancy. So, I think some sort of strong advice is necessary because I think a lot of people will

let social considerations prevent them from properly excluding pregnancy in certain instances.

DR. EAGLSTEIN: Further comments or discussion on this point? What we are leading to is a vote on whether or not there should be changes, not what they will be, but whether or not further revision in the labeling concerning these teratogenic effects is necessary.

And what I have heard so far that if the answer were to be yes, that people might want to say, should be for pregnancy test, they might want to put a box there, and they might want to say an alternative could be a 28-day prescription. Those are the things that have surfaced in our discussion.

DR. KENNEY: Mr. Chairman, I would like to move that there should be a change.

DR. EAGLSTEIN: Okay.

DR. KOEHN: Second.

DR. EAGLSTEIN: Okay. For the formality, I think we should vote on the question and then go to the revisions that we want. We're saying that there should be further revisions.

MR. BOSTWICK: All right, okay.

DR. POMERANZ: Second.

DR. EAGLSTEIN: Okay. Everybody ready for the vote. We are going to vote on whether or not there should be further revisions in the labeling.

All those in favor of further revisions?

(A show of hands.)

DR. EAGLSTEIN: All against?

(No response.)

DR. EAGLSTEIN: I don't think there is anyone left. So, that is 6-0 vote to say that there should be revisions.

Would someone like to make a motion, or move a specific revision? Does someone have a specific revision in mind?

DR. RASMUSSEN: Can we accept basically what the FDA has suggested to us in general as one vote, and then discuss the pregnancy testing as a separate vote? Because I think the only issue we're discussing here is not the little two-page handout in general, but the little sentence about pregnancy testing. Can we do that? Can we discuss this one item and go to the next?

DR. EAGLSTEIN: I'm not sure I am following you.

DR. RASMUSSEN: In other words, can we adopt this whole thing, this two-page memorandum, which was handed to us when we came in, which is the FDA's suggestion for labeling, which I think we all agree with with the exception of --

MR. BOSTWICK: The second page has to do with the patient insert, Dr. Rasmussen. The first page had only to do with what we're discussing now.

DR. EAGLSTEIN: The first is the physician insert.

So, you're suggesting that we accept all four of those paragraphs?

DR. RASMUSSEN: Except the portion that deals with the pregnancy test, which is in the third or the second sentence in paragraph one. It says, "The pregnancy test should be performed no longer than two weeks before onset of Accutane therapy."

And then we can discuss that as a separate sentence.

DR. EAGLSTEIN: I don't think the first two sentences, or the first sentence has changed from the current wording, has it?

MR. BOSTWICK: No, it hasn't. What he wants to do is to adopt everything except this one sentence and then discuss that sentence separately.

He wants to buy all this -- these next three paragraphs.

DR. EAGLSTEIN: I think in question is to teratogenicity, and we should stick with that. Now, we said we want to change the label and we need to say how we want to change it. I don't think it's -- if we adopt these other issues, we haven't really discussed them.

Well, as I have said, what has been suggested, there have been several suggestions that we can box the current one or any other one. That we should have a pregnancy test, or that we could say, may be given every 28 days, or after the

menstrual period.

Would anyone like to propose adopting any of these revisions since we've said there is a need for revision?

DR. WOLFE: The vote was whether there is a need for a revision of the present labeling or from what the FDA proposed.

DR. CHANCO-TURNER: On the present labeling.

Page 2 on --

DR. EAGLSTEIN: Dr. Rasmussen, I gather that in adopting the -- not to adopt the pregnancy test, you would would be really happier with the present labeling?

DR. RASMUSSEN: I didn't say that. I just said that as far as I'm concerned, we haven't had any significant dissention among us on any of the items on this first sheet. except the pregnancy issue. Now, your correction to that is that we have only been discussing teratogencity.

DR. EAGLSTEIN: Right.

Does anyone --

DR. CHANCO-TURNER: May I move?

DR. EAGLSTEIN: -- please do?

DR. CHANCO-TURNER: I would like to move that we accept the FDA revision on the warning, reading, "Because abnormalities of the human fetus have been reported, it is recommended that contraception be continued, et cetera. A pregnancy test should be performed no earlier than two weeks before

onset of Accutane therapy."

DR. EAGLSTEIN: Is there a second?

DR. RASMUSSEN: I second it.

DR. EAGLSTEIN: All right. May I ask, is this clear, "no earlier than two weeks?" Am I living too far from Washington? It doesn't instantly have meaning to me.

DR. RASMUSSEN: It must be within two weeks from the time you start the drug.

DR. EAGLSTEIN: I know. I'm saying, is that well said? Does everyone -- when you read that, does that just come right through to you?

DR. KOEHN: She didn't include that in her move?

DR. CHANCO-TURNER: I did.

DR. EAGLSTEIN: She did.

DR. KENNEY: Yes, she did.

DR. EAGLSTEIN: But I am just saying that that wording I find quite awkward.

DR. KENNEY: I don't like "no earlier."

DR. EAGLSTEIN: No earlier.

DR. CHANCO-TURNER: Within two weeks.

MR. BOSTWICK: Within.

DR. CHANCO-TURNER: Within two weeks.

DR. EAGLSTEIN: That is wha I was referring to.

DR. CHANCO-TURNER: I took it to mean within two weeks.

DR. EAGLSTEIN: Okay.

MR. BOSTWICK: Within two weeks before? Leave in the word befor?

DR. CHANCO-TURNER: Within two weeks of onset of Accutane therapy.

DR. TABOR: This is a small point, but that could mean two weeks in either direction.

DR. CHANCO-TURNER: Before.

DR. TABOR: Prior to?

DR. CHANCO-TURNER: Prior to.

MR. BOSTWICK: Now, read me the whole thing, Dr. Turner, I'm lost in the switches here?

DR. CHANCO-TURNER: A pregnancy test should be performed within two weeks prior to onset of Accutane therapy.

MR. BOSTWICK: Okay.

DR. EAGLSTEIN: Okay. So, that's a proposal. It has been seconded. Moved and seconded.

Is there a discussion on that? This is really that it should be performed. That we have in a way discussed it already.

Are you ready for the vote. All those in favor of this motion which would say, "should be performed." "The test should be performed."

All those in favor, please raise their hand?

(A show of hands.)

DR. EAGLSTEIN: Three.

All those opposed?

(A show of hands.)

MR. BOSTWICK: You get to vote.

DR. EAGLSTEIN: Four. I get to vote to make a tie.

(Laughter.)

DR. HASERICK: It is three four and three against. What is your vote?

DR. EAGLSTEIN: I am voting for this motion. So, I make it a tie.

MR. BOSTWICK: Let's go through one more time.

DR. EAGLSTEIN: Who is in favor of it, in favor of the motion? And I will be voting.

(A show of hands.)

DR. EAGLSTEIN: Against it?

(A show of hands.)

DR. EAGLSTEIN: Four and four. So, that is not a revision that we have agreed upon.

MR. BOSTWICK: It is not.

DR. HASERICK: Back to the drawing board.

DR. TABOR: May a suggest a compromise, which includes as an alternative the administration immediately after onset of menstrual period?

DR. CHANCO-TURNER: A discussion on that. From what I remember of my obstetrics, it is not unusual for women

during their first two months of pregnancy to bleed.

DR. RASMUSSEN: That's true.

DR. CHANCO-TURNER: Just when they are expected to menustrate --

DR. RASMUSSEN: But it usually is not as heavy as a normal menstrual period.

DR. CHANCO-TURNER: -- yes, but then you have to get into how heavy, how many tampons.

DR. GOLDNER: A compromise might be though just the insertion of strongly recommended. If you make that strongly recommended.

DR. RASMUSSEN: How about a pregnancy test is one of the most reliable ways to ascertain pregnancy, or something like that.

DR. POMERANZ: Well, you could put a pregnancy test within two weeks prior to Accutane is extremely important.

DR. GOLDNER: I am not objecting to the concept; I'm really objecting to that little word "mandatory."

DR. CHANCO-TURNER: What about the others --

DR. POMERANZ: What about the lipid studies, and that sort of thing. If, any thing, the lipid studies are less valuable. Nobody knows what triglycerides mean.

DR. GOLDNER: Well, but when this Committee originally met that problem, we were aware of the triglyceride elevations and we all wanted to know them prior to and during

our treatment because of the potential risk to that. I mean, that was agreed to at the time.

DR. POMERANZ: But the potential risk of triglyceride elevation and possible coronary artery diseases is miniscule compared to the problem of the woman getting pregnant.

DR. RASMUSSEN: But there is no other way of assaying the triglyceride and cholesterol level other than doing laboratory tests. There are other ways that you can discover, or at least have some indication of whether a patient is pregnant and that is simply talking to people. There is -- that system is not useful in determining cholesterol levels or triglycerides.

So, this is not the only way that you can get around that problem.

DR. CHANCO-TURNER: Except the potential damage, the potential impact of a birth defect is so much more serious than a transitory elevation of triglycerides.

DR. RASMUSSEN: I think we all agree it is a useful test. Why don't we devise some sort of wording that would convey that opinion without pressing people to do it.

DR. KENNEY: Mr. Chairman, two of those who vote in opposition say they are willing to go along with it as strongly recommend that pregnancy test; so, I so move that revision.

DR. EAGLSTEIN: Okay.

DR. RASMUSSEN: Would you read that specific sentence,

John?

DR. KENNEY: Okay, I'll try. It is strongly recommended that a pregnancy test should be performed within two week prior to the onset of Accutane therapy.

DR. RASMUSSEN: I could go for that.

DR. EAGLSTEIN: That's seconded.

Dr. Rosa, from the FDA.

DR. ROSA: I would like to point out that if you do a pregnancy test at the time of onset and it is negative; then, the woman was not pregnant two weeks or even six months. She's not carrying a pregnancy.

DR. GOLDNER: Would you repeat that?

DR. ROSA: If you did a pregnancy test at the time you start the Accutane and the woman is not pregnant; then, she was not pregnant. She is not carrying a pregnancy that she had prior to start Accutane.

DR. GOLDNER: That's what all that means is that she was not pregnant prior to starting it.

DR. ROSA: So, there is no advantage to doing it two weeks prior. You need to do it at the time, as close as possible to the time of administering the Accutane.

DR. GOLDNER: Oh, I see your point. I see your point. is that two weeks --

DR. KENNEY: He suggests even closer.

DR. TABOR: The only advantage of two weeks is that

it gives the physician more flexibility of when it's done and where it is done.

DR. EAGLSTEIN: Okay. Would you read us the motion again?

MR. BOSTWICK: As I understand Dr. Kenney's sentence, it is that a pregnancy test is strongly recommended within two weeks prior to onset of Accutane therapy. Is that correct, Dr. Kenney?

DR. KENNEY: It is strongly recommended that a pregnancy test should be performed within two weeks prior to the onset of Accutane therapy.

MR. BOSTWICK: Oh, I see.

Is there any further discussion?

(No response.)

DR. EAGLSTEIN: All those in favor of this motion, which is, what, strongly recommended?

MR. BOSTWICK: Yes. It is strongly recommended that that a pregnancy test should be performed within two weeks prior to onset of Accutane therapy.

DR. KENNEY: Just take the should out and it will be all right.

MR. BOSTWICK: Take the should out.

DR. EAGLSTEIN: Okay. All those in favor of adopting this motion as a recommendation?

(A show of hands.)

DR. EAGLSTEIN: And those opposed?

(No response.)

DR. EAGLSTEIN: I think we are unanimous.

Okay. Now, are there further suggestions?

DR. BILSTAD: Are you clear now, was that with the should or without the should?

DR. EAGLSTEIN: No. That's with the strongly recommended.

DR. BILSTAD: Well, there is also a should in there.

DR. KENNEY: We agreed to drop the should.

DR. CHANCO-TURNER: It is strongly recommended.

DR. EAGLSTEIN: So, the should has been dropped and strongly recommended inserted.

Now, do you want to amend this, or suggest revisions of any other sort?

(No response.)

DR. EAGLSTEIN: Does anyone want to move that they be placed -- this information be placed in a box as was requested by the petitioner?

DR. RASMUSSEN: I don't see anything wrong with that. I think the problem is that this is going to sit at the end of a page and a half --

DR. CHANCO-TURNER: On page 2.

DR. RASMUSSEN: -- I presume that these are the way the pages will actually sit. That this is the type that --

so it would be down -- about a third of the way down the second page, and if I were doing this, I would either box it or stick it at the top, or put it as a --

DR. POMERANZ: If it could be put at the top.

DR. RASMUSSEN: -- because this is the big thing that you are talking about right now and putting it down here, it loses a little of its impact. I think that would be impossible to overlook if you put it right under the name, or something like that.

DR. EAGLSTEIN: So, you want to move its position, is that what you're saying?

DR. RASMUSSEN: I would be comfortable with that. I would like to know how other people feel.

DR. EAGLSTEIN: You want to move it to where, again?

DR. RASMUSSEN: Well, whatever. I don't know the particular format for listing drugs, but I would stick it some place close to the top. I don't know if it would go under the name --

DR. EAGLSTEIN: On the front page? One of the first places of information?

DR. RASMUSSEN: Right up under the heading Accutane; so, if you saw the word, you would see the warning.

DR. EAGLSTEIN: Okay. And in a box?

DR. POMERANZ: In red.

(Laughter.)

MR. BOSTWICK: I don't think we can do that.

DR. EAGLSTEIN: And in a box, is that what you are saying?

DR. RASMUSSEN: That's what I would do.

DR. EAGLSTEIN: Do you want to develop a motion?

DR. RASMUSSEN: I will move that this warning paragraph which we have amended and approved be placed in a box in prominent bold type. I don't know where to say to put it. Of course, under the name if it can be done.

DR. EVANS: Ahead of the description section?

DR. RASMUSSEN: Ahead of the description, all right.

DR. POMERANZ: Second.

DR. EAGLSTEIN: All right. It's been seconded. Is there a discussion on this point?

(No response.)

DR. EAGLSTEIN: Do you want to vote. All those in favor, raise your hand?

(A show of hands.)

DR. EAGLSTEIN: All those in opposition?

(No response.)

MR. BOSTWICK: You only got six that time.

DR. EAGLSTEIN: It's unanimous.

Okay. Are there other suggestions for revision of this label as regard to teratogenic effects?

DR. RASMUSSEN: I do not know if it is important

to discuss it now, but we have discussed the issue of how we can as reasonable as possibly rule out the possibility that a patient is pregnant at the time the drug is presented. Do you think we should address the question of the fallibility of contraceptives other than abstinence? In other words, if people are going to be on this drug and you do it hundreds of thousands of times, somebody is going to get pregnant even with all these precautions. Do you think we should make that as a statement? Or would that be better left for consideration of a patient handout item?

DR. CHANCO-TURNER: What, that we make a statement?

DR. RASMUSSEN: The idea that even if you use contraceptives, there is no fool proof system, and even though severe acne is a moderate contraceptive in its own right, there is going to be a problem. If you use it long enough, somebody is going to get pregnant. And I'm wondering if we should discuss that as an issue? Somebody is going to have to face the problem of being pregnant even though they are doing all these precautions?

DR. CHANCO-TURNER: You are not going to suggest abstinence?

DR. RASMUSSEN: Oh, no, I wasn't dealing with that at all, but I was just wondering if we ought to remind people that somebody is going to be in this dilemma of being pregnant and on Accutane even though they are using adequate contraception.

DR. EAGLSTEIN: Do you want that in the physician's insert or the patient's insert?

DR. RASMUSSEN: If I were going to put it some place, I would probably put it in the patient's insert so that somebody, at least, has the emotional or the option of deciding that if they get pregnant, they may have to make a tough decision about abortion, although it won't be very likely. It would only be 1 percent. But if you do 300,000 people, 1 percent is, what, 300?

DR. EVANS: It's a good point.

DR. RASMUSSEN: If it is half of them, 250.

DR. EAGLSTEIN: Do you want that in the physician's insert?

DR. RASMUSSEN: I don't know. I was just bringing that up as a discussion. It is something that concerns me.

DR. EAGLSTEIN: In one of the -- it may be in the patient's, it says, "If you accidentally get pregnant, let your doctor know."

DR. KOEHN: Yes, right.

DR. EAGLSTEIN: And you could say that since it is possible to get pregnant even with using birth control pills, or birth control methods, let your doctor know. But is that in the doctor's insert?

DR. KOEHN: It is here again.

DR. EAGLSTEIN: What page?

DR. KOEHN: Page 2. It is about the third paragraph down. Women of child bearing age. "The should be fully counseled on the potential risk to fetus should they become pregnant while undergoing treatment. If pregnancy does occur during treatment, the physician and patient should discuss the desirability of continuing the pregnancy."

DR. EAGLSTEIN: Jim, do you want to put in there somehow that since all birth control or since most birth control --

DR. KOEHN: No, that sentence is satisfactory. I think it is fine.

DR. EAGLSTEIN: -- okay. So, that satisfies your concern in that area?

DR. RASMUSSEN: Yes.

DR. EAGLSTEIN: Any other areas of revision that people would like to discuss or suggest for the teratogenic effect?

Dr. Koehn?

DR. KOEHN: Under contraindications, the first sentence, "Patients who are pregnant or who intend to become pregnant while undergoing treatment" --

(Laughter.)

DR. KOEHN: It seems that it should say, "or who may become pregnant," rather than intend to.

DR. EAGLSTEIN: So, you are suggesting that this be altered?

DR. KOEHN: Instead of "who intend to," to say, who may become pregnant.

DR. EAGLSTEIN: Who may become pregnant.

DR. KOEHN: I move that under contraindications, the first sentence be changed to "Patients who are pregnant or who may become pregnant while undergoing treatment must not receive Accutane."

DR. RASMUSSEN: I'll second the motion.

DR. KENNEY: I'll second the motion.

Is there is a discussion on this?

DR. RASMUSSEN: Yes. May is a very nebulous problemmatic word. Anybody may become pregnant while taking Accutane, any woman even using contraceptives.

DR. EAGLSTEIN: Well, not if she's not of child bearing potential.

DR. RASMUSSEN: Well, then she wouldn't be on Accutane.

DR. EAGLSTEIN: She might.

DR. RASMUSSEN: Who could possibly be on Accutane that wouldn't be of child bearing potential?

DR. EAGLSTEIN: Well, they may have had a hysterectomy or something.

DR. RASMUSSEN: All right.

DR. EAGLSTEIN: I think that is what you mean. If you have the chance. If you are able to become pregnant.

DR. RASMUSSEN: Well, that could be interpreted to exclude every woman who hasn't had a hysterectomy, because anybody could become pregnant while taking Accutane. Any woman who still has a uterus and an ovary.

DR. EAGLSTEIN: I see.

DR. RASMUSSEN: In other words, none of these systems we are talking about are infallible even tubal ligation has a failure rate.

DR. EAGLSTEIN: I see what you're saying.

DR. RASMUSSEN: In other words "may" is a word that indicates possibility.

DR. EAGLSTEIN: I see. And this is a contraindication, must not receive.

DR. RASMUSSEN: Right. So, you literally interpret that, anybody who had any potential for becoming pregnant, that is, anybody who is having sex and has a uterus and an ovary would be contraindicated. You could interpret that if you were a very strict constructionist to mean that no woman who could possibly conceive could use this drug ever.

DR. CHANCO-TURNER: Uh-huh.

DR. RASMUSSEN: And that is not what I think you are intending to say, is it?

DR. KOEHN: Okay. I take my motion back and I move that we strike that first sentence under contraindictions.

DR. POMERANZ: It is redundant in a way. It really

is not clear. The entire sentence --

DR. EAGLSTEIN: Do you take away your second?

DR. KENNEY: I'll take away the second.

DR. EAGLSTEIN: Do you want to move to strike the entire sentence or do you want to leave it contraindicated for those who are pregnant?

DR. POMERANZ: I think women should come in and say they have cystic acne and they were thinking of having a baby.

DR. EAGLSTEIN: So, you think that it is clear as it stands.

DR. CHANCO-TURNER: As a matter of fact --

DR. POMERANZ: I think the sentence is very clear. It means they are planning on getting pregnant. It is something they are looking for.

DR. CHANCO-TURNER: -- as a matter of fact, I didn't start a patient on Accutane for that very reason.

DR. EAGLSTEIN: All right. Now, what motion do you want to make. I think there isn't a motion.

DR. CHANCO-TURNER: Just leave it there.

DR. EAGLSTEIN: All right.

MR. BOSTWICK: Leaving it there.

DR. EAGLSTEIN: Other proposed revisions to this teratogenic effect?

(No response.)

DR. EAGLSTEIN: I had -- these are minor, but it

seemed to me that in the -- that the heart and micro-ophthalmia had been left out of the reported birth defects list.

DR. RASMUSSEN: These were animal birth defects. They were showing human data.

DR. EAGLSTEIN: Oh, those were only animal.

DR. EVANS: They probably hadn't been reported at that time.

DR. EAGLSTEIN: So, I would like to ask someone to move that they be placed in for completeness unless you think that's being --

Jerry, would you move that?

DR. POMERANZ: I move that they be.

DR. EAGLSTEIN: The list of things that have occurred and I think this is quite minor, but the way we've been told that heart defects and some microophthalmia or small eyes have occurred as well. So, I think that to complete the picture for the physician.

DR. KOEHN: And spontaneous abortion is not --

DR. EAGLSTEIN: Now, where does the abortion fit in, the spontaneous abortion. Is that put in here anywhere?

DR. KOEHN: -- no. I didn't see it. I just wondered if you are going to include the others, if that should be included.

MR. BOSTWICK: Well, it is not really a fetal

abnormality, which is what you are listing there.

DR. EAGLSTEIN: Can we put this in as a fetal abnormality and then if you want to find a place for that, an appropriate place. We can suggest placing that as well?

DR. RASMUSSEN: Well, it is probably certain that the reason the fetus was aborted was because it had a fetal abnormality.

DR. EAGLSTEIN: So, you think it should be here?

DR. RASMUSSEN: Yes.

DR. EAGLSTEIN: So, your motion, Dr. Pomeranz, would be for all three?

DR. POMERANZ: Yes.

DR. EAGLSTEIN: To include heart and small eye birth defects and abortions.

Can we just vote to have these things added in the appropriate place?

MR. BOSTWICK: You sure can.

DR. EAGLSTEIN: Since this is real minor.

All those in favor of adding this information where it seems appropriate?

MR. BOSTWICK: Which is heart defects, microophthalmia, and birth defects.

DR. EAGLSTEIN: Right. Please say yes.

(Show of hands.)

DR. EAGLSTEIN: All right.

And one other thing I want to ask the Committee, the next sentence is (2) on the insert, page 2, the fourth paragraph, it tells about the rats and all that. I don't know what that tells the doctor that is helpful. I just don't -- maybe I just don't get it. You tell about the doses for the rat and the problems, but --

DR. RASMUSSEN: Well, they have far more experience with presumably hundreds or maybe thousands of laboratory animals and these are the observations that they have made implying that these are the types of things that might potentially occur letting people know that they are very serious.

You have already said that they are serious in your second paragraph. I don't see anything wrong in leaving it in there.

DR. EAGLSTEIN: Well, it dilutes the other information.

DR. RASMUSSEN: Yes, but as more human experience comes about, these things may also be seen in people.

DR. EAGLSTEIN: All right. Is that what everyone feels? Leave that there?

DR. CHANCO-TURNER: Uh-huh.

DR. DR. BILSTAD: I would also make the point that if you get concurrence between animal studies and the human data that perhaps is stronger.

DR. EAGLSTEIN: All right.

DR. BILSTAD: In other words, you are finding the same finding in both places.

DR. EAGLSTEIN: Okay. Now, does anyone else have a suggestion or suggestions as to what further revisions concerning teratogenic effects are necessary?

(No response.)

DR. EAGLSTEIN: Okay. If there are none, let's turn to question number two.

Question number two is: does the information on the occurrence of pseudotumor cerebri in patients undergoing Accutane therapy warrant a more prominent display in the package insert?

MR. BOSTWICK: It is presently in the adverse reactions.

DR. EAGLSTEIN: It's on page 3.

MR. BOSTWICK: Okay.

DR. EAGLSTEIN: Near the bottom of page 3 and where else?

MR. BOSTWICK: I think that's the only place we have it.

DR. EAGLSTEIN: It's the third paragraph from the bottom And the question is: does the Committee want to recommend that this information be more prominently displayed?

DR. KOEHN: Yes.

DR. EAGLSTEIN: Any discussion?

DR. HASERICK: We have already agreed on this.

DR. POMERANZ: Yes. We have already agreed on this.

MR. BOSTWICK: We can take a formal vote and then we will be done with it.

DR. EAGLSTEIN: And actually, I think we can probably go further. This just says, do you want it displayed. It doesn't say do you want to change the words in any way.

MR. BOSTWICK: No. All it says, is do you want that information in a different place?

DR. EAGLSTEIN: Do you want it displayed more prominently. I gather you want to vote on that?

DR. HASERICK: It isn't necessary from my point of view because I approved the whole thing except for that pregnancy question.

DR. EAGLSTEIN: All right. So, you will vote yes?

DR. HASERICK: Yes.

DR. EAGLSTEIN: Would someone move that we vote on question two?

DR. POMERANZ: I move we vote on question two.

DR. GOLDNER: Second.

DR. EAGLSTEIN: All those in favor --

DR. RASMUSSEN: Wait. Can we have a little discussion?

DR. EAGLSTEIN: Yes.

DR. RASMUSSEN: I just want to make it clear to everybody what we are discussing is not this two-page handout, but on page 3 under tab F, paragraph 3 from the bottom. It starts, "Cases of pseudotumor cerebri." That is what we are voting on, not FDA's suggestion. This is the company's proposed revised package insert, or whatever you want to call this thing. Physician insert, whatever. That is what we are voting on. We are not voting on this sheet at all.

DR. EAGLSTEIN: We are voting on displaying it more prominently.

DR. GOLDNER: I am a little confused on that. I didn't realize that's all we were voting on.

DR. CHANCO-TURNER: The question is this.

DR. RASMUSSEN: The question is, tab F, page 3, paragraph three from the bottom. It starts, "Cases of pseudotumor cerebri." We are talking about whether we want it displayed in a different fashion or place.

MR. BOSTWICK: That's correct.

DR. EAGLSTEIN: If you say yes, then you have -- then it says, "What are your suggestions?" You might suggest changing the words at that point.

MR. BOSTWICK: Right.

DR. EAGLSTEIN: Are we ready we vote.

All those in favor of saying that they want to

have it displayed more prominently, raise their hand?

(A show of hands.

DR. EAGLSTEIN: All opposed?

(No response.)

DR. EAGLSTEIN: I think it is unanimous.

Okay. Since the answer is yes, what suggestions do we have for implementing these changes, this change, and I think it could be a change in words as well as place, bold type, box, whatever. And I think it should be pointed out that the petitioner asked for a box again. Is that true?

DR. RASMUSSEN: Bill, I would like to move that we adopt, as stated, the second paragraph of this memorandum from David Bostwick to the Dermatology Advisory Committee Members, which begins, "Accutane use has been associated," and substitute that for the insert -- I mean the tab F, page 3, the one we just voted on. And the second part of that motion is that we put it underneath the previously described warning on teratogenicity which we've just discussed; that is, at the top of the area in a box in bold type, because the two main problems that we are discussing here today are teratogencity and pseudotumor cerebri. And there is no reason why people shouldn't read about those things right off the bat.

DR. EAGLSTEIN: First of all, may I ask that you -- can we do those one at a time?

DR. RASMUSSEN: Sure. I first move -- my first motion is to adopt, as written, this FDA suggested paragraph, which begins, "Accutane use has been associated," and include in that to replace this paragraph three, page 3, tab F form.

DR. POMERANZ: I'll second the motion.

DR. EAGLSTEIN: Any discussion on this? I must say, I thought as a matter of wordage, pseudotumor cerebri, it says, "The signs and symptoms" and then it says, "include intercranial hypertension," which I don't think is a sign or a symptom. And I thought maybe the way around that would be to say, "Pseudotumor cerebri (intercranial hypertension) are detected by papilledema."

Do you see what I'm trying to say? That it is not really a sign or a symptom. It is maybe a mechanism or a finding that you can come across if you do the proper test.

But that again is minor. The sense of what is being said is that we adopt this warning.

MR. GOLDSMITH: Bill, with this new paragraph there is no discussion of possible tetracycline interaction.

DR. EAGLSTEIN: That's right.

MR. GOLDSMITH: It dilutes that point.

DR. EAGLSTEIN: Which is in the current -- I think it is in the current statement, and I think that this FDA proposal is fairly consistent with the petitioner's proposal. It's almost exactly.

DR. GOLDNER: The problem with including it is that it dilutes the meaning again. The physician tending to think if my patient is not on tetracyline when I have her on Accutane, that in fact, I don't have to worry as much.

DR. EAGLSTEIN: So, you feel that this is the right way to go?

DR. GOLDNER: Right. I think so.

DR. EVANS: You could also put it in the precaution section, "Precaution if used in association with tetracycline and the following might occur."

DR. EAGLSTEIN: Well, could I get some feeling as to whether you would consider an amendment of your motion so that hypertension isn't a sign or a symptom?

DR. POMERANZ: It wouldn't bother me.

DR. GOLDNER: Could we get a reading from our neurologist of his interpretation of that. Is that clear to you?

DR. CORBETT: I'm sorry, I didn't hear the question.

DR. EAGLSTEIN: Well, as the wording -- the wording that's been proposed says that, "Early signs and symptoms of pseudotumor cerebri include intercranial hypertension," and the question is: is that a sign or a symptom?

DR. GOLDNER: It is not a sign or a symptom. It is a diagnosis.

DR. CORBETT: And your question is?

DR. EAGLSTEIN: Is that a sign or a symptom?

DR. CORBETT: No, but neither is pseudotumor cerebri.

DR. EAGLSTEIN: No, we know that. But what are the signs and symptoms of pseudotumor cerebri?

DR. CORBETT: Intercranial hypertension is a sign only when you do a lumbar puncture.

DR. EAGLSTEIN: So, it is good enough for you?

DR. CORBETT: But it is not a sign when you are just examining the patient.

DR. EAGLSTEIN: What do you suggest?

DR. CORBETT: My suggestion would be that you put in parenthesis (Accutane has been associated with a number of cases of pseudotumor cerebri) and put in parenthesis, (increased intercranial pressure).

DR. EAGLSTEIN: That is what I suggested.

DR. CORBETT: Because pseudotumor cerebri dignifies it with a name. There are a lot of people who argue about that whether that should be the name.

DR. EAGLSTEIN: Whose motion is this now?

(Laughter.)

DR. EAGLSTEIN: Can the Committee amend your motion?

DR. RASMUSSEN: Go ahead.

DR. EAGLSTEIN: Any objection?

DR. RASMUSSEN: Go ahead.

DR. EAGLSTEIN: Okay. Do you understand this?

MR. BOSTWICK: I understand that we are going to -- the first sentence of this paragraph is now going to read, "Accutane use has been associated with a number of cases of pseudotumor cerebri." And we're going to put in parenthesis, (increased incranial pressure).

DR. EAGLSTEIN: Right. As another name for pseduo-tumor cerebri?

MR. BOSTWICK: All right. And what are we going to do about the second sentence?

DR. EAGLSTEIN: No, it's -- "Are detected by pappiledema."

MR. BOSTWICK: All right. So, we are going to take that out.

"As detected by," right.

All right. So, the -- I think we've got the motion on the floor; it's seconded. Any further discussion?

(No response.)

DR. EAGLSTEIN: This does exempt the tetracycline part. So, this is a motion on the words.

All those in favor -- do you want to vote. All those in favor of these words?

(A show of hands.)

DR. EAGLSTEIN: All those opposed?

(No response.)

DR. EAGLSTEIN: So, we are suggesting that the words be changed to -- that this motion will substitute -- the words in this motion will substitute for the words currently in the physician's insert.

Jim, do you want to read them?

DR. RASMUSSEN: You want me to read the --

DR. EAGLSTEIN: "Accutane has been associated with a number of cases of pseudotumore cerebri. Early signs and symptoms of pseudotumor cerebri (intercranial hypertension) are detected by papilledema, headache, nausea and vomiting." And then it is the continuation of what the FDA proposed.

MR. BOSTWICK: Okay.

DR. EAGLSTEIN: Okay, Jim, your second motion.

DR. RASMUSSEN: My second motion was to take this paragraph and put it under the one that we just finished voting on about teratogenicity so that both of them will be in both typed in a box at the top of the insert under -- or before description. In other words, this would be item number two.

DR. EAGLSTEIN: Okay. Is there a second to that motion?

DR. POMERANZ: I'll second.

DR. EAGLSTEIN: Discussion?

(No response.)

DR. EAGLSTEIN: Does the FDA have a posture on this, or is this an unusual way to do things?

MR. BOSTWICK: We want to know what the Committee wants to do?

DR. EAGLSTEIN: I understand that. I just want to know if this is --

DR. EVANS: It can be done either way. We have done it both ways.

DR. EAGLSTEIN: -- okay.

Now, you did not indicate the box?

DR. RASMUSSEN: Yes, I did. In the box, item number two, under teratogenicity.

DR. EAGLSTEIN: All right. Is there a discussion on this?

DR. GOLDNER: We are giving equal severity to the two problems, that's what we're doing by boxing them and putting them in the beginning of the insert. We are giving equal status to the two.

DR. CHANCO-TURNER: Should we?

DR. GOLDNER: Should we? That's the --

DR. EAGLSTEIN: That's what we are going to vote on now.

DR. RASMUSSEN: Well, those two seem to be the most prominent side effects that we know about today from the reasonably short-term use in the treatment of acne. Now,

other problems may arise for people who were using it for a longer term, for second courses, but I think that these are the two items that are the most important to people. And we are not giving them equal weight, or we would put them without numbers. If you put (1) and one (2), it is like who gets top billing the theatre. It's not that they are both super --

DR. EAGLSTEIN: Okay.

DR. RASMUSSEN: -- I think these are the things you want people to notice. You really want to emphasize that, and that's where you are going to do it as an item right under the number of the drug. It would be hard to overlook.

DR. EAGLSTEIN: Further discussion?

DR. DEL VECCHIO: Mr. Chairman, may I make a suggestion?

DR. EAGLSTEIN: Please do?

DR. DEL VECCHIO: I would just like to echo what has been said here. I think the possibility of diluting the pregnancy warning, despite the fact that you put this in a black box, is very real. And the more boxes that you have up front, the more likely you are to dilute the most important factor here, which is the prevention of pregnancy.

Let me suggest an alternative, which is to leave it in place in the adverse reactions area and put it in bold print to make it stand out in that particular area so that it is more prominently displayed.

DR. EAGLSTEIN: All right. We are discussing putting it second in a box in bold print and we've heard the suggestion that if we defeat that idea, we might put it in a box in bold print --

MR. BOSTWICK: Not in a box, just in bold print.

DR. POMERANZ: Just put it in bold print as number two.

DR. EAGLSTEIN: All right. That was the suggestion that it be put in bold print as number two rather than as the box. I thought I heard it --

DR. POMERANZ: Oh, no, that's what you did hear, but I'm just saying --

DR. EAGLSTEIN: -- oh, okay.

DR. POMERANZ: -- if there is objection to the box, just use bold print.

DR. RASMUSSEN: I would find that quite acceptable so long as it maintains a prominent place. I would not feel very comfortable sticking it down --

DR. POMERANZ: It is way down at the bottom now.

DR. RASMUSSEN: -- in warnings because quite honestly most people never get passed the name of the drug and the dosage. That's about the only two things that people read. It's hard to overlook that type of a warning if it iw right under the name. It would be fairly easy to overlook it if it were down among six or eight or ten other problems.

DR. EAGLSTEIN: Uh-huh.

DR. RASMUSSEN: So, I would like to see it up at the top. I don't care if it is in a box or not. If somebody feels it will dilute it; then, I would be glad to amend to taking it out of the box, but still keeping it prominently displayed at the top of the description.

DR. EAGLSTEIN: Well, why don't you leave your motion on the floor. If they want to defeat; then --

DR. BILSTAD: I am not sure that we have ever allowed a warning at the beginning of labeling that is not in a box. I think if we put it at the beginning of labeling normally, we do put it in a box.

DR. EAGLSTEIN: So, the standard format is that if it is at the beginning, it is in a box?

DR. BILSTAD: That's my impression. I'm not aware that -- you can put a box elsewhere in the labeling. There have occasionally been boxes in the warning section, but I think it might be confusing if you had both a box in one case and simply the bold face print in the other case and both of them were at the beginning at the label.

DR. EAGLSTEIN: Other comments?

DR. GOLDNER: That was my point, too. I'm not familiar with any other labeling that I've seen where it has been a (1) (2). If -- the Methotrexate, or whatever else you have is a box warning, it's there, but you don't have then

something under that that further warns. We would be going against what has been done in the past.

DR. TABOR: I would just like to add my opinion which is that I think it would dilute the pregnancy warning to put it up front. I think even though there have been too many cases of pseudotumor cerebri, it is still a rare complication and that putting it in bold print at the beginning of the warning section should be adequate.

DR. EAGLSTEIN: Bold print at the warning section?

MR. BOSTWICK: Right. Just move it out of adverse reactions and put it at the top of the warnings.

DR. EVANS: And that's FDA's suggestion.

DR. EAGLSTEIN: That's FDA's suggestion. All right. Any further discussion on this motion?

(No response.)

DR. EAGLSTEIN: Do you want to withdraw this motion, or would you like us to vote on this motion? I had suggested you leave it.

DR. RASMUSSEN: I don't mind going down in flames, leave it.

(Laughter.)

DR. EAGLSTEIN: All right. The motion that is before is that these words, which we've adopted, be placed in a box in bold type at the beginning after the warning about teratogenicity.

DR. RASMUSSEN: That's correct.

DR. EAGLSTEIN: And this is the pseudotumor.

So, all those who favor doing that, who favor adopting that recommendation, raise their hand?

DR. BILSTAD: One question before. Are you talking about one box or two?

DR. EAGLSTEIN: I thought we were talking about two boxes. Am I right or wrong?

(A show of hands.)

MR. BOSTWICK: Did I get four yes on that vote?

DR. BILSTAD: Yes, you did.

DR. EAGLSTEIN: And all those opposed?

(A show of hands.)

DR. EAGLSTEIN: I think we've got it.

DR. BILSTAD: Did you vote on that?

DR. EAGLSTEIN: No, I didn't. I would have tied it.

MR. BOSTWICK: The Chairman has a vote. You're a member just like anybody else.

DR. EAGLSTEIN: I know. I think, however, that there is something unsettling about tying because we don't solve the --

DR. RASMUSSEN: We tie it and go back some other way.

DR. HASERICK: That means there is something wrong with it.

DR. EAGLSTEIN: Well, I'll tie that one.

So, we just tied that and, therefore, I guess did not adopt the motion to put these words in a box in bold type at the beginning.

So, does anyone want to move for another approach.

DR. GOLDNER: I would like to move that we leave the box warning on pregnancy in the beginning and add the warning for pseudotumor to the bold type at the beginning of the warning section.

DR. POMERANZ: I'll second that.

DR. EAGLSTEIN: In a box or out of a box?

DR. POMERANZ: Bold type out of the box.

DR. GOLDNER: Can we put it in a box in the warning section?

DR. POMERANZ: That's the one --

DR. GOLDNER: No, the warning section. There's a difference between putting it in the warning section and putting it at the beginning of the --

DR. POMERANZ: -- I think you can put it in the box there.

DR. GOLDNER: You can. Then, I would still make my motion to say in a box in the warning section.

DR. EAGLSTEIN: Okay. So, this is a motion that these words which we have adopted on pseudotumor be left -- be placed in the warning section at the beginning of the warn-

ing section and in bold type and a box.

DR. GOLDNER: Correct.

DR. CHANCO-TURNER: I second the motion.

DR. EAGLSTEIN: Any discussion?

(No response.)

DR. EAGLSTEIN: All those in favor?

(A show of hands.)

DR. EAGLSTEIN: All opposed?

(No response.)

DR. EAGLSTEIN: Well, we've got three more to go, but I don't know how much time they will take. The lunch place closes at 2:00 if its the cafeteria; so, why don't we just take a half hour. Let's be back at 1:30.

(Whereupon, at 1:00 p.m., the meeting was recessed, to reconvene at 1:30 p.m.)

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AFTERNOON SESSION

(1:30 p.m.)

DR. EAGLSTEIN: The meeting will come to order.

Okay, now, number three is: does the Committee recommend any other adjustment to the labeling of Accutane? And the FDA position had been that corneal opacity warning should be placed and that there should be a warning about Chron's disease. And I think that the petitioner had the same concerns. Opacities and Chron's.

So, I guess we could do this in the same way. Do you want to vote each yes or no, and then if it is yes, to go over which items you want to add?

MR. BOSTWICK: Let me make a comment about Chron's disease. I know that the people that wrote this position is that this is not Chron's --

DR. EAGLSTEIN: Right, ileitis.

MR. BOSTWICK: -- it is ileitis instead.

DR. EAGLSTEIN: It is duly noted.

Is everybody ready to vote on number three? Somebody move that we accept a vote on number three.

DR. RASMUSSEN: Can I have a point of clarification before we get to voting?

DR. EAGLSTEIN: Yes.

DR. RASMUSSEN: Will someone who knows tell me if I am wrong in believing -- when I heard the presentation that

said that corneal opacities had only occurred in patients who had keratinizing disorders who were on higher doses than we would normally use. Is that correct or incorrect?

DR. EAGLSTEIN: Is there anybody here from Roche that can address that?

DR. CUNNINGHAM: The original NDA contained several patients with disorders of keratinization who had corneal opacities and those were resolved after Accutane was discontinued.

In addition, in the post-marketing period, we've had now three patients with cystic acne develop corneal opacities. As I mentioned, those have tended to resolve as well off therapy. In fact one resolved while the patient was still on Accutane therapy and discontinuation of his contact lenses.

DR. RASMUSSEN: Were those visually symptomatic lesions?

DR. CUNNINGHAM: No, they were not visually symptomatic.

DR. RASMUSSEN: How were they ascertained, just on screening for other problems, or what?

DR. CUNNINGHAM: One patient complained of dryness and the eyes were looked at. The patient had some eye dryness, and the corneal opacities were noted. It is a coincidental finding. And including the source of

keratinization had been reviewed. I think it is acceptable in terms of the dry eye syndrome that one sees with the drug, but not very common.

DR. EAGLSTEIN: Okay. So, as regards question number three, is there any more discussion?

(No response.)

DR. EAGLSTEIN: I think we can assume that it is a motion.

DR. RASMUSSEN: I would like to discuss it a little more.

DR. EAGLSTEIN: Right.

DR. RASMUSSEN: Either before or after it is made a motion.

DR. EAGLSTEIN: Why don't you make it a motion?

DR. RASMUSSEN: Well, because I don't want to get shot down in flames again.

(Laughter.)

DR. RASMUSSEN: I don't mind doing it. My personal feeling is that if the corneal opacities have not interferred with vision. They have only been picked up because of an eye exam for some other problem as dryness and keratitis, something like that, and if they have resolved after the drug has been discontinued that I don't feel that an ophthamological exam is necessary. The way this second sentence in this third paragraph reads, "All Accutane patients should receive routine

ophthamologic exams." If that means that somebody should look in their eyes, that's one thing. If it means that an ophthamologist should look in their eyes, that's another thing. My personal opinion is that it is not necessary to do that. This is not a major problem. It doesn't interfere with vision and it is resolved spontaneously. I would be against that.

DR. EAGLSTEIN: So, you, as regards corneal opacities, would not favor the FDA proprosal?

DR. RASMUSSEN: I think you could make the statement in the warning section or in the adverse reactions, or wherever you wanted to put it that corneal opacities have occurred in the patients receiving Accutane. But then the next sentence, I disagree with, and I disagree fairly strongly saying that all Accutane patients should receive routine ophthamological exams.

It doesn't appear to be major. It appears to resolve on its own. It doesn't interfere with vision.

DR. EAGLSTEIN: Did you want to amplify this?

DR. CUNNINGHAM: I want to spea to that a little bit. We did have in the original NDA, 280 patients who had baseline and follow-up eye exams and you had that data previously to look at, and, in fact, the yield is rather low, other than conjunctivitis there are very few side effects that have been picked on those screening exams. So, that would

support it, correct.

DR. EAGLSTEIN: Did those exams include slit lamp?

DR. CUNNINGHAM: Yes, they did.

DR. EAGLSTEIN: And that was more --

DR. CUNNINGHAM: And retinal exam.

DR. EAGLSTEIN: -- that was more than a dermatologist might do?

DR. CUNNINGHAM: Oh, yes, absolutely. They included examination of all the segments of the eye, including the retina.

DR. GOLDSMITH: I think the problem is with the word "ophthamological" that implies ophthamologist and I think another word like "eye" was inserted in there that might --

DR. RASMUSSEN: I wouldn't even feel that that was necessary because they've done 200 of these with an indepth eye exam and their post-marketing results have indicated no major problems, it doesn't bother me.

DR. CHANCO-TURNER: Mr. Bostwick, was it your intent to require an ophthamologic exam prior to starting or only if they have signs and symptoms?

I understood it to mean --

MR. BOSTWICK: I understood it to mean signs and symptoms.

DR. CHANCO-TURNER: -- signs and symptoms.

MR. BOSTWICK: I did not write this. How is that?

I do not know whose intent it was to do write it.

DR. EAGLSTEIN: Dr. Goldner?

DR. GOLDNER: Again, if we go to Section F, page 3, there is already an approved warning there at the bottom of page 3 that corneal opacities have also been reported in cystic acne patients which is the intent of Jim's wording. He would like that noted in the package insert without the recommendation for ophthamologic. That's the last paragraph on page 3 of Section F.

DR. RASMUSSEN: That would be sufficient for me as long as it is in there. The final part of that sentence says, "And Accutane should be discontinued immediately if they experience ophthamological signs or symptoms." That means that everybody that gets a little dryness of their eyes, you are going to have to stop the program. I don't stop it for that. I keep right on going. I tell them to use artificial tears or take their contact lenses out. I've never had any significant trouble with that.

DR. EAGLSTEIN: In some of the information we received, there were cases with visual loss that didn't seem to be related to pseudotumor. Were they related only to the opacities or weren't there some that just had visual loss and we just don't know why?

DR. CUNNINGHAM: There are two different phenomenon in here. The corneal opacities have never resulted in any

visual loss either in the disorders of keratinization patients in the NDA or in the post-marketing cystic acne patients.

DR. EAGLSTEIN: Okay.

DR. CUNNINGHAM: Now, as far as visual loss, I talked about that this morning in terms of that being one of the manifestations of pseudotumor cerebri. Of course, that's a rather common presenting symptom of pseudotumor cerebri.

Am I correct, that part?

DR. CORBETT: It's transient.

DR. CUNNINGHAM: It's transient, yes, okay. Transient episodes of blurring vision, but permanent visual loss is very uncommon. Very uncommon.

DR. EAGLSTEIN: I am asking about the petitioner's statement that eight additional cases and 30 percent decrease in one eye and 50 percent decrease in the other.

DR. CUNNINGHAM: That patient is the patient that I mentioned this morning. That was the only one --

DR. EAGLSTEIN: Was that the pseudotumor?

DR. CUNNINGHAM: -- no, that patient had visual loss secondardy to post-encephalitis.

DR. EAGLSTEIN: Okay.

DR. CUNNINGHAM: And we have had a couple of others that have had blurring of vision, for example, but not documented visual loss. Blurring of vision has resolved on its own. So, in essence, when we separate out only the pseudotumor cerebri

with some sort of visual disturbance. We have one other patient with documented visual loss which, after the encephalitis was over, resolved.

DR. EAGLSTEIN: Thank you. Are there other comments? We are discussing number three and actually we're discussing specific ideas as to what might still be adjusted. And on these opacities, we've had several comments. Are there more on opacities, or do you want to discuss any other adjustment? The ileitis is another proposed adjustment.

DR. RASMUSSEN: Why don't we do them one at a time, Bill, so it won't be so confusing?

DR. EAGLSTEIN: All right. We are not really answering number three right now --

MR. BOSTWICK: You can always answer it no.

DR. EAGLSTEIN: -- right. We are going to discuss the opacities in preparation and we're going to discuss the ileitis in preparation for answering number three. Are there any other areas that we need to address? Will there be any other suggested changes? In your reading of the label proposals, have you seen other areas that you wanted to --

DR. KOEHN: With question tetracycline with --

DR. EAGLSTEIN: --with tetracycline, okay.

Any others?

DR. HASERICK: There is one little bit of ambiguity on page 3 of F, the final line says, "Corneal opacities have

been reported in the cystic acne patients." You could view that and interpret that almost as a disclaimer that as seen in cystic acne patients, and you don't know whether they have been treated with Accutane or not. So, I think we ought to tag that with treatment of Accutane on the end of it so there is no ambiguity. It sounds as though they are saying, oh, it's nothing. It happens in cystic acne patients anyway. But what they really mean, that it comes on after Accutane.

DR. EAGLSTEIN: Okay. We will have that as a possible change, treated with Accutane.

Are there other areas. Now, ileitis, we have heard a lot about it, Chron's disease, ileitis. Do you want to discuss this. Is this an area that the FDA proposals that are being added in the warnings, and it is paragraph four on the memo from Mr. Bostwick. Ileitis is in the package insert.

MR. BOSTWICK: It is listed in a group of other --

DR. EAGLSTEIN: It is called inflammatory bowel disease, including regional ileitis. And the petitioner and the FDA are more or less congruent on this.

I don't get this sense of urgency about this ileitis. Was it just that you were worn out, or it is not so important?

DR. GOLDNER: Does the percentage still hold? Is it 1 percent, less than 1 percent still correct from the petitioner's point of view and FDA? I mean, is everybody

agreeing on that that it is less than 1 percent?

DR. EAGLSTEIN: Is anybody disagreeing?

(No response.)

DR. EAGLSTEIN: I guess so.

Shall we vote first on number three, should we recommend other adjustments, and then on the four areas that we've -- well, tetracycline, you really haven't told us what about tetracycline you want to do?

DR. KOEHN: Well, it was taken away.

DR. EAGLSTEIN: Right.

DR. KOEHN: You know, concomitant use of tetracycline.

DR. EAGLSTEIN: Should it be put back in?

DR. KOEHN: That's what I'm asking. I don't really know.

DR. EAGLSTEIN: I thought Dr. Goldner had expressed the opinion that it was mitigated.

DR. GOLDNER: Okay. We took it away because we didn't want to dilute the warning with Accutane and we said that we could put it in back here, you know, to emphasize the fact that there is a relationship between the two. I certainly have no problem with that. I think that would be warranted.

DR. EAGLSTEIN: Is that a fact that there is a relationship, or is it a fact that half the people did take --

DR. GOLDNER: Somebody's slide showed that, or somebody's data showed that that was presented this morning.

DR. CUNNINGHAM: As I mentioned, 10 patients with pseudotumor cerebri and/or papilledema, and out of those, five have been on concomitant tetracycline or minicycline, but it is rather difficult to say, of course, with any certainty that it is or is not related other than the fact that they are being used concomitantly.

DR. EAGLSTEIN: They were both in the same patient.

DR. CUNNINGHAM: I think as Dr. Corbett pointed out this morning, however, it is rather uncommon with tetracycline and there are large numbers of patients receiving tetracycline; so,I think there is no question that Accutane causes this syndrome. The question is, is it exacerbated? Is there any synergistic action on tetracycline? And I don't know that they can make a firm establishment of a relationship there.

DR. EAGLSTEIN: Okay.

Dr. Koehn, you are suggesting that words be entered saying that they may -- there may be a greater chance of this if both drugs are taken. Is that what you're saying?

DR. KOEHN: I'm saying they may, yes. But I got that from Dr. Strauss, not today but other times when he has presented that several of these cases were on tetracycline. And if that be the case; then, I think that the physicians should know that this is a possibility that they are being synergistic, and -- I don't know.

DR. CHANCO-TURNER: Can you just make a non-

committal statement that while the 10 cases of pseudotumor cerebri were on concomitant tetracycline or minicycline.

DR. EAGLSTEIN: Well, the question, I think, is, do you read this to mean to suggest that Accutane may not be the cause, or do you want to say that it is the combination that is the cause?

DR. CHANCO-TURNER: I think I am only saying that we don't know.

(Laughter.)

DR. CHANCO-TURNER: But that it has been.

DR. EAGLSTEIN: All right. So, let's vote on number three and then go into the four areas we have outlined.

Number three is: does the Committee recommend any other adjustments to the labeling of Accutane?

Ready to vote. All those in favor, raise their hand?

(A show of hands.)

DR. GOLDNER: We've added "were treated with Accutane." We have to vote in order to get that in there.

DR. EAGLSTEIN: Against?

(No response.)

DR. EAGLSTEIN: Everyone is for it.

Now, the four, the corneal opacities, the other items, the tetracycline and the addition of these words.

So, starting with corneal opacities, which would be

the stickiest one, the proposal that the FDA and the petitioner gave us is in the third paragraph. Do you want to vote on adopting this? Does somebody want to move to adopt it?

DR. RASMUSSEN: I would like to move that it not be adopted.

DR. KENNEY: I'll second that motion. I thought we agreed that what was here was adequate.

DR. EAGLSTEIN: All right.

I think we might be wise to propose adopting it and then defeat that proposal.

DR. POMERANZ: I move that it be adopted.

DR. EAGLSTEIN: We're looking for a second.

DR. RASMUSSEN: I'll be glad to lead it to the execution.

(Laughter.)

DR. EAGLSTEIN: Are we ready to vote or is there a discussion?

(No response.)

DR. EAGLSTEIN: We're voting on the proposal that we adopt the statement, the third paragraph, that corneal opacities have occurred in patients and that everybody should receive ophthamologic exams and discontinue it immediately if they experience signs or symptoms.

All those in favor?

(Show of hands.)

DR. EAGLSTEIN: All those opposed?

(A show of hands.)

DR. EAGLSTEIN: Okay. The motion fails.

Is there any change that should be made as regards this corneal opacity issue from the current statement which is in the last sentence, the last two sentences on page 3, accepting that many people will probably vote to change that, as Dr. Haserick has suggested, but leaving that aside, do you want to strengthen this in one some way, but change it in some way?

DR. HASERICK: We just voted not to.

DR. EAGLSTEIN: Is there a motion to that effect?

(No response.)

DR. EAGLSTEIN: Then, let's move on.

DR. GOLDNER: Oh, we just want to vote to add the words --

DR. EAGLSTEIN: We will. Okay. I'm sorry. Let's go ahead and do what you say now.

Then, there is a motion. Do you want to make this motion, Dr. Haserick, to change this?

DR. HASERICK: Additional words?

DR. EAGLSTEIN: To add the words, "treated with Accutane?" To the final sentences on page 3. "Corneal opacities have been reported in cystic acne patients treated with Accutane."

DR. HASERICK: Yes, right.

DR. EAGLSTEIN: Second.

DR. GOLDNER: Second.

DR. EAGLSTEIN: Discussion?

(No response.)

DR. EAGLSTEIN: All those in favor?

(A show of hands.)

DR. EAGLSTEIN: Opposed?

(No response.)

DR. EAGLSTEIN: It carries, "treated with Accutane" added.

We are moving to regional ileitis, also known as Chron's disease, or is it Chron's disease also known as ileitis?

The FDA proposal is the final paragraph which is very similar to the petitioner's, and the current statement is: on page 3 of the insert, and it is called inflammatory bowel disease. It is one of the side effects and it has a paranthesis (including regional ileitis.)

DR. GOLDNER: I would propose for the inclusion of that paragraph with the elimination of "Chron's disease" from it.

DR. EAGLSTEIN: So, you would --

DR. GOLDNER: I would propose, "Accutane use has been associated with regional ileitis in patients without a prior history," et cetera.

DR. HASERICK: Second.

DR. EAGLSTEIN: Now, that includes patients experiencing abdominal pain, rectal bleeding, severe diarrhea discontinue immediately.

MR. BOSTWICK: This would be left in the adverse reaction section, Dr. Goldner? Or would you put it in warnings?

DR. GOLDNER: Yes.

DR. EAGLSTEIN: Okay. Let's just go to the words first.

MR. BOSTWICK: Okay.

DR. EAGLSTEIN: Moved and seconded.

Discussion?

DR. KOEHN: What happened to colitis?

DR. CHANCO-TURNER: It's not there.

DR. EAGLSTEIN: We left it out.

DR. GOLDNER: Wait a minute. Tell me what I did?

DR. EAGLSTEIN: She wants colitis.

DR. HASERICK: It's never been in there.

DR. GOLDNER: No, I didn't see that in here.

DR. CHANCO-TURNER: It was in the People's -- whatever the --

DR. EAGLSTEIN: Ws it in the petitioner's suggestion?

DR. CHANCO-TURNER: -- I think it was in the petitioner's suggestions.

DR. GOLDNER: But I didn't see any data presented on that today.

DR. EVANS: Four or five cases, but it is not in

the insert.

DR. GOLDNER: Well, if the data was there, I missed it. Then, I certainly would like to include it, but I just don't remember seeing that.

DR. EAGLSTEIN: Do you want to insert these?

DR. CUNNINGHAM: I might point out that the present wording does include both, and it is still correct; that is, it is less than 1 percent of patients have experienced. It's in that paragraph. The next to the last sentence on the package insert, "Inflammatory bowel disease" -- this includes colitis, of course --

DR. EAGLSTEIN: Okay.

DR. CUNNINGHAM: -- and then "(including regional ileitis.) And I would propose that it be left in that context because we have looked at this rather thoroughly. I have given you some of the information on particular cases this morning as well, and I did not see anything other than a temporal relatioship with this particular effect at this time and I think it is misleading to tell the practitioner otherwise at this point in time.

DR. EAGLSTEIN: Okay. So, you propose not changing the insert from its current status?

DR. CUNNINGHAM: That's right.

DR. EAGLSTEIN: Thank you.

The motion that Dr. Goldner made is to adopt this

statement, paragraph 4 of the FDA position, deleting Chron's disease.

Now, Dr. Koehn, did you want to amend his motion or ask for an amendment?

DR. KOEHN: No. I was just curious why --

DR. EAGLSTEIN: Dr. Goldner, do you want to amend your motion?

DR. GOLDNER: You mean to state just inflammatory bowel disease, or rather just to -- well, no, I think I'd like to make the motion the way it is and see what this Committee feels about putting that strong a warning for this.

The only thing we might say, "Accutane use has been associated with inflammatory bowel disease (regional ileitis)." If you'd like to do that; then, that takes in the colitis cases also. It does make it a stronger warning than the way it is now.

DR. EAGLSTEIN: Would you like to do that? "Inflammatory bowel."

DR. GOLDNER: Yes.

DR. EAGLSTEIN: Who is your second? Is that all right?

DR. HASERICK: Second.

DR. EAGLSTEIN: Okay. Any other discussion?

(No response.)

DR. EAGLSTEIN: So, this is a motion to adopt this

statement which would displace the current statement and presumably strengthen it and suggest more of a relation than the sponsor feels exists.

Other discussion?

DR. KOEHN: So, you are just proposing to take out of here, "inflammatory bowel disease, mild GI bleeding, weight loss," or what are you taking out to put this in?

DR. EAGLSTEIN: Right now we are not taking much. We are just going to add this statement and, I guess, by implication later, you could take out something.

DR. KOEHN: You're just going to --

DR. EAGLSTEIN: But this motion is to add, I think. Although the question says adjust.

Any other discussions?

(No response.)

DR. EAGLSTEIN: All those in favor?

(Show of hands.)

DR. EAGLSTEIN: All those opposed?

(No response.)

DR. EAGLSTEIN: That's been adopted as the recommendation.

So, I think those are the four, it's tetracycline --

MR. BOSTWICK: I have one other question. Is this inflammatory bowel disease paragraph to stay in adverse reactions?

DR. EAGLSTEIN: That's a good question, because we had put that aside as to where it would belong. The FDA's recommendation was warning. It currently stands under, what, adverse reactions.

What does the petitioner think?

DR. GOLDNER: Where is this under?

DR. EAGLSTEIN: And the petitioner wants it under warning.

DR. CHANCO-TURNER: Well, a lot of these things are both in warning and adverse reactions. How do you make a decision as to which goes where?

DR. EVANS: It depends on how serious you think it is. Contraindictions is most severe and precautions is much less.

DR. BILSTAD: Normally, it needs to be in the adverse reaction section and if it is serious, you put it in the warning section. You can, if you have more information in one place than the other, and don't put the same information in both places, just simply refer to the other section. For example, you can say, see warning section.

DR. EAGLSTEIN: But right now it is in the adverse reactions which would be less significant presumably than those above, is that right, the precaution and the warning?

DR. BILSTAD: Uh-huh.

DR. EAGLSTEIN: Now, Dr. Goldner made the motion.

Did you have a feeling on that?

DR. GOLDNER: Yes. My feeling was that it belongs under adverse reactions really rather than warnings, where it is. I think that it needs to replace the words that are there. I think it is another paragraph, but to strike out what is said here under, "The following reactions have been reported less than 1 percent and may bear no relationship to therapy." I think we have reason to believe that it is a stronger warning than that, but I really don't believe it belongs on page 2. I would like to insert it there and strike out "inflammatory bowel disease" from that paragraph.

DR. EAGLSTEIN: Let's have two motions. The first one to strike "inflammatory bowel disease."

Second, Dr. Kenney?

DR. KENNEY: Yes, I'll second it.

DR. EAGLSTEIN: All those in favor?

(A show of hands.)

DR. EAGLSTEIN: All those opposed?

(No response.)

DR. EAGLSTEIN: Okay. It passes.

Now, what is the next one, to add this --

DR. GOLDNER: That I would make a motion to add this paragraph in the appropriate part of adverse reactions?

DR. EAGLSTEIN: All right. The motion is that these words, which we have adopted, should be placed in the adverse

reaction section.

Any discussion?

DR. GOLDNER: Second.

DR. EAGLSTEIN: All those in favor?

(A show of hands.)

DR. EAGLSTEIN: Opposed?

(No response.)

DR. EAGLSTEIN: It is unanimous.

Tetracycline as an addition. Does anyone want to move adding the thought about tetracycline and the -- I guess in the pseudotumor cerebri?

DR. KOEHN: I'm not ready to make a motion, but I must say from the people who have used it the most, they tell us that.

DR. EAGLSTEIN: They'd tell you anything.

(Laughter.)

DR. KOEHN: And I believe it. I think that that should be passed on from the people who have had the most experience if indeed it is. It's been in there before.

DR. TABOR: The real difficulty is that where it was before was supposed to tone down the statement about pseudotumor cerebri. There are now additional cases, and both FDA and the company feel that at least some of the pseudotumor cerebri cases are clearly not associated with concomitant use of tetracyline. So, to add it back to the pseudotumor

tumor cerebri portion or anywhere near it would serve to delete the warning about pseudotumor cerebri. And from what was said a few minutes ago, it sounds that the only data to suggest an additive effect of tetracycline and pseudotumor cerebri, the only real data is -- I'm sorry, the only data to suggest an additive effect of tetracycline and Accutane is the pseudotumor cerebri data and possibly also theoretical additive effect because we know that both have been associated with pseudotumor cerebri independently. So, I think it is a mistake to put it with the pseudotumor cerebri because it dilutes it further and that is what we were trying to avoid by taking it out.

The only question is: do you have enough data to put it anywhere else in the labeling.

DR. EVANS: If you look under the precaution section, the top of page 3, it shows, "precautions, information for patients." And "Because of relationship with Accutane to vitamin A, patients should be advised against taking vitamin supplements containing vitamin A to avoid additive toxic effects."

It seems to me this is the same kind of thing you talked about.

DR. EAGLSTEIN: You are suggesting you could say "and tetracycline to avoid additive toxic effects."

DR. EVANS: Or.

DR. EAGLSTEIN: That seems to me to be a big jump though because the idea of the tetracycline was that it might have been a cause of pseudotumor independently. And now were are going to give the opposite notion that together there is a great chance. I don't think there is any reason to believe that is true, is there?

DR. TABOR: Well, there is a theoretical basis in that tetracycline alone can be associated with pseudotumor.

DR. EAGLSTEIN: So, you think the two added together.

DR. TABOR: Yes.

DR. EAGLSTEIN: I see what you are saying.

DR. TABOR: But it is purely theoretical. From what I have heard this morning, I don't think there is any hard data --

DR. KOEHN: Either way.

DR. TABOR: -- either way.

DR. EAGLSTEIN: Would that compromise the physician trying to treat acne patients?

MR. GOLDSMITH: We heard from Dr. Strauss this morning that he tries to get his people off minicycline, tetracycline and to get them on to a Erthromycin and with his experience we would suggest that there is some usefulness from his --

DR. EAGLSTEIN: Is that because the Erthromycin doesn't cause pseudotumors?

Let's get Dr. Strauss to help us out?

DR. STRAUSS: As has been pointed out from the head of the table, that is purely theoretical, and there is no hard data to support that. It is purely a theoretical gut feeling and so, I don't think there's any data there.

DR. EAGLSTEIN: Is that true for vitamin A as well, that is theoretical?

DR. TABOR: No.

DR. EAGLSTEIN: It is experimentally proven?

DR. CUNNINGHAM: Well, it is not experimentally proven, but the molecules are so closely related in terms of their chemical structure and in terms of their effect and side effect profile that even though we don't have data to support that --

DR. EAGLSTEIN: But it's theoretical too?

DR. CUNNINGHAM: -- the conclusion would obviously be that one should not take extra vitamin A on top of Accutane to prevent the additive effects. With tetracycline, we're talking about two entirely different classes of compounds, retinoids and tetracycline. The question, as I see it, cannot be resolved now, but just a simple statement puts some perspective on it, that is that five of the ten cases have been associated with tetracycline or minicycline. And I don't think any of us could make a firm judgment at the present time as to what the relationship might be, but it does warn the physician to some extent.

DR. EAGLSTEIN: So, you would favor putting something in about tetracycline, concomitantively?

DR. CUNNINGHAM: Yes. Not to dilute the pseudotumor cerebir. I agree entirely with Dr. Tabor on that, but to at least bring it up as a point for thought to the practitioner.

DR. TABOR: Without suggesting any particular course of action, I would say that I think the theoretical concerns about tetracycline are probably greater than the concerns raised by the data that you have because -- I mean, I think everybody is agreed that some of the cases of pseudotumor are Accutane related and those who are on both medications, you really have no data to support any allegations of tetracycline interacts with or adds to the effect of the Accutane.

But the theoretical concern that the tetracycline alone can cause pseudotumor and the Accutane alone apparently, in some cases, can cause pseudotumor cerebri, I think is worth perhaps bringing out -- I'd almost be more in favor of something -- stating something about the theoretical concerns than stating something specifically about pseudotumor cases which might detract from the pseudotumor warning.

DR. EAGLSTEIN: You would favor something like since tetracycline and Accutane both have been associated with, they should not be used together.

DR. TABOR: Yes. The physician should use caution in deciding to use tetracycline at the same time.

DR. EAGLSTEIN: Dr. Koehn, do you have some words? Do you want to write something down and propose that we adopt it?

DR. KOEHN: Okay. If I could say, I was just concerned, you know, it seems like a real thing to be concerned about and physicians reading this and not seeing tetracycline mentioned anywhere, I'm afraid we may have more cases of pseudo-tumor cerebri.

DR. EAGLSTEIN: Give us something to vote upon, to accept or reject?

DR. KOEHN: Okay. Give me a minute until I find my way here.

DR. EAGLSTEIN: All right.

While you are doing that, let's move to number four in the discussion phase. Number four is: how can the patient package insert, which is the one -- now, in this case, the patient package insert -- this is the insert we've been discussing, isn't it?

MR. BOSTWICK: No, that's the physician package insert. Why don't we call it the leaflet. It's easier to separate them that way.

DR. EAGLSTEIN: So, now, we are moving to the next insert, which is the voluntary patient package insert, the one that has had 600,000 or something. And what we have before us is one that lists some proposed changes, is that correct?

DR. BILSTAD: Yes.

DR. EAGLSTEIN: And we also have the FDA proposal, which they call the patient leaflet, and the petitioner had a further set of suggestions.

MR. BOSTWICK: I don't think so.

DR. EAGLSTEIN: The petitioner just had the idea that it should be mandatory?

DR. CHANCO-TURNER: That is should be mandatory.

DR. EAGLSTEIN: On page 7, patient package insert recommendation.

DR. POMERANZ: But it recapitulates is all that I got from it.

DR. EAGLSTEIN: Right. It does. But he has a lot about the lipids and the heart problem on page 8. That the patient is supposed to ask the doctor to reduce the dose after two weeks. On page 8 of the petitioner's letter, the bottom paragraph. Actually, it was a more extensive set of suggestions.

DR. CHANCO-TURNER: It does go into doses of less however.

DR. EAGLSTEIN: Right. He wants the patient to be told to tell the doctor to give them less.

DR. CHANCO-TURNER: Yes. I also have a question mark on that.

DR. EAGLSTEIN: Right. So, we are discussing -- it's a qeneral question. It doesn't call for a vote. It says:

How can the package insert prepared by the drug sponsor be made more effective? Maybe you've looked through it and make some remarks, or maybe you'd like to go point by point through the FDA's suggestions and go through the petitioner's suggestions. What would be your pleasure?

DR. CHANCO-TURNER: We also have to address the petitioner's?

DR. EAGLSTEIN: I don't think you have to.

MR. BOSTWICK: You don't have to, but they are there, and if you have something to say about them, you should feel free to.

DR. CHANCO-TURNER: Well, on page 9, there is something that says, "Labeling fails to state that permanent loss of vision can result from pseudotumor cerebri," and we've just heard that it is not true. There is no permanent loss of vision from pseudotumor cerebri.

But he wants this to go in the box.

DR. EAGLSTEIN: No. I think there can be. I think no one has said it. It could occur.

DR. POMERANZ: It occurred in the past, but not today.

DR. EAGLSTEIN: Not with current treatment.

DR. CHANCO-TURNER: Right.

DR. EAGLSTEIN: Well, the petitioner has the most extensive list of suggestions. Do you want to go through that, or do you want to go through the one as it stands?

DR. GOLDNER: This is as corrected, isn't it? Is this the one that they are correcting?

DR. EAGLSTEIN: They are amending, right.

MR. BOSTWICK: That leaflet there is not presently available.

DR. EAGLSTEIN: Let's go through it as it is and see what you see -- what your notes say if you have any, and go to the FDA and to the petitioner.

Looking at the amended patient, does anyone have any thoughts on the very first page, which is the page that says that background color is going to be blue.

(Laughter.)

DR. GOLDNER: The important thing is that they are changing a message to important information.

DR. EAGLSTEIN: Okay. They're going to do that.

DR. GOLDNER: They're doing to do that.

DR. EAGLSTEIN: So, you're not --

DR. GOLDNER: Which I would agree with.

DR. EAGLSTEIN: -- okay. Next page. That's about the acne. The next page. This is a change of a warning to the female patients. Now, this does not mention pregnany test.

MR. BOSTWICK: I think when you get into the next page before treatment, you'll --

DR. POMERANZ: It's also in the FDA thing.

MR. BOSTWICK: Oh, that's right. It's in the FDA