effect. However, lo-percent dropout with constipation is a quite dramatic number, too. The only other thing I'd like to bring up that is related to ischemia that I meant to mention is it would be very nice to see flat plates, tbdominal x-rays of people; you know, i.e., in a smaller lumber of people who get constipation, do they actually develop a non-toxic mega colon and have secondary problems. So I think that would be something I'd want to follow up both related to (a) and (c).

DR. WILSON: I basically agree with the prior comments. I don't think the constipation would be a major problem because it was an easy prohibition and it was reversible, it appeared, quite simply.

CHAIRMAN HANAUER: I would assume that it's related to the drug.

[Laughter.]

DR. FERRY: I don't see that as a problem in the approval process.

DR. GELLER: I don't either, but I certainly think it has to be mentioned.

CHAIRMAN HANAUER: Yes.

DR. WILSON: I was going to say that it is, I mean, because they weren't aiming to study that group.

CHAIRMAN HANAUER: Okay, nitty-gritty time. In view of the data presented, do the potential benefits of

alosetron therapy outweigh its potential risks for the proposed indication; i.e., do you recommend the compound be approved? And then based on that, we have some subsidiary questions.

So we'll let Dr. Geller start. Do you think should be--Dr. Geller, do you think it should be approved?

DR. GELLER: Yes.

DR. FERRY: Yes, I do.

CHAIRMAN HANAUER: Yes.

DR. WILSON: Yes.

DR. LAINE: Okay.

DR. BERARDI: Yes.

CHAIRMAN HANAUER: You don't get to vote.

DR. WALD: Yes.

[Laughter.]

CHAIRMAN HANAUER: The next component says if not, what additional--we've said yes, but I think we should say do we need additional efficacy or safety data from the sponsor. And I will let Dr. Wald answer that. What additional--even if it's going to be approved, what should we be requesting? Do you want more data on liver toxicity, do you want more data on ischemia, that kind of stuff--pediatric data, old-age people?

DR. WALD: Well, I certainly would like to see more pharmacokinetics in women. I think the point was made

earlier that the early studies on pharmacokinetics were done in men. I certainly think we need to monitor the drug closely for side effects, particularly the ischemic issue. I'm not so worried about the constipation because it's going to be there, and the liver. I want to see the quality of life data. I think that will be very important. And as just my opinion, in a disorder such as this, I think we should be using that as one standard of looking at a drug like this.

DR. HOUN: Could I ask if these additional studies should be performed prior to approval or after approval?

DR. WALD: I think based upon what I've seen, I think we could approve the drug with the caveat that we monitor it very carefully and with the expectation that what complications we've seen have not proven too injurious. So I would not hold up the approval pending that data.

CHAIRMAN HANAUER: Dr. Berardi, any comments, additional studies that you would like to see?

DR. BERARDI: No.

DR. LAINE: Besides all the obvious safety stuff, I agree with quality of life very importantly. The'one thing again I say, as a clinician I want to know how long I'm going to need to keep this patient on it before I decide it does or doesn't work. That's why I asked that question earlier. You know, do I give it to them for a month and, if

it doesn't work, stop? I think that kind of information would be very important to me. This is a long-term--these people are going to be on it a long time, but perhaps there may a subset that do and don't respond and I'd like to know how long I have to wait to determine that.

CHAIRMAN HANAUER: I'm not so unclear on that. I interpret the data showing that if they don't respond, they're not going to respond, both by virtue of the three-month total response, all or none, as well as the transitional probabilities that we heard about.

DR. LAINE: Well, it looks to me that if they don't respond at a month, they are unlikely to respond beyond a month, is what I'm saying.

CHAIRMAN HANAUER: That's my interpretation.

DR. LAINE: But I'd just like to have that made clear to me, and I think they have the data and can do that. But that's kind of how I read the data, but I'd really like to know that just to help me manage patients clinically.

CHAIRMAN HANAUER: Dr. Wilson?

DR. WILSON: I don't think there are any specific additional studies, namely, though, as Dr. Wald said, close monitoring prior to or during the early phases. I don't know how that is regulated, but that would be my recommendation.

CHAIRMAN HANAUER: Phase IV studies.

I would just add in that because this drug is going to be potentially applied to such a large population, I think that the what appear to be small numbers have a significant chance of being amplified, and particularly the colitic complications and the liver enzymes just need to be watched in the expanded database. And I would certainly want to see as large a database as possible from the sponsor.

DR. LAINE: So would they.

DR. FERRY: I think the only--I mean, the really significant thing I'd like to push would be really careful documentation of any kind of colitis-like picture so we really can clarify what the problem is.

DR. GELLER: I'd like to see the results of the year study. I think that that gives much better data on long-term use than we have.

CHAIRMAN HANAUER: Before it's approved?

DR. GELLER: That's a good question.

CHAIRMAN HANAUER: What's your opinion? They want your opinion.

DR. GELLER: I'm not sure, I'm not sure. One of the problems is that the only time we have seen that data was today. That's not included in the book, so it would be harder to get a really clear view.

CHAIRMAN HANAUER: The obvious question is how

close are we to getting that data. If it's next week, it's going to be a different issue. Do we--how long until the one-year data is going to be available? And if I were you, I'd say 12 months.

DR. MANGEL: Well, I assume you're referring to the 12-month--

CHAIRMAN HANAUER: Long study.

DR. MANGEL: --safety data, not efficacy data.

DR. LAINE: Right, 12-month safety data.

DR. MANGEL: I believe in your briefing document there actually was data included from the 12-month-long safety study--

CHAIRMAN HANAUER: Until it's completed?

DR. MANGEL: --as to interim analysis. Actually the study is completed now and we do have draft tables. I can't tell you the results of it. We certainly didn't present it because it would have been new information for the FDA that they did not see. The pattern was identical for completion of the study as it was in the second interim analysis, which were the data which you saw and have included. Once again, there were no cases of ischemic colitis reported in the 12-month-long safety study. At the end of the day, that 187 number for completion of 12 months of treatment was now over 300 for 12 months of treatment.

CHAIRMAN HANAUER: Yes, Dr. Wald?

DR. WALD: I'm just thinking about this. I wonder if there's any data about practical use of this drug. There's nothing to say that these patients should be taking it forever, and since IBS is an intermittent, recurrent problem, I wonder if there's any study going on to give open-label drug to patients with IBS to see how they use it, to give them the option, then, of one, two, or nothing on a given day or a week *or* something to see what patterns might be established, because patients may well not want to take it everyday even though their symptoms may return. And that might be very important in the post-therapeutic trial to see how we might ourselves begin to use this, let our patients be our guide.

DR. MANGEL: You know, we actually do not have an episodic design study underway, Dr. Wald.

DR. WALD: You do?

DR. MANGEL: No, we do not.

DR. WALD: And I'm thinking of another drug in another setting where that is being used, and that might provide very useful data over a year to see how patients would use it and whether that would make a difference.

CHAIRMAN HANAUER: Okay. The last question is what labeling recommendations does the Committee have to reduce the potential risks of alosetron, and I'll let Dr. Laine answer that first. He's in the middle.

DR. LAINE: To reduce risk, I mean again basically you want to--

CHAIRMAN HANAUER: How do you think it should be labeled first?

DR. LAINE: Right. I mean, basically it should be Labeled for female patients. Obviously, it should be only those who have no hard stool, no constipation or diarrhea, depending on how you want to suggest that. I would probably say no hard stool and no constipation. And I think until we get more information, we have to at least mention especially the colitis issue, say that incidences of colitis were seen. Its association is unclear, but, you know, it requires further study. If something becomes more clear in the next month or two when the information is reviewed by the agency, then that should be incorporated.

CHAIRMAN HANAUER: My two cents, and then we're going to zig-zag, is that I think that the labeling should be for treatment for females with irritable bowel whose predominant symptom is diarrhea, period. I don't think that there is sufficient efficacy, nor do I think that the risk has been--I think the risk is higher in those with alternating, by all that we've discussed, and I would not include alternating stool pattern in the indication.

Dr. Wilson, comments?

DR. WILSON: Yes. I would agree with those

statements, basically, to focus on diarrhea. I'm not sure what language would be most correct, certainly, but to focus on diarrhea.

CHAIRMAN HANAUER: Dr. Berardi?

DR. BERARDI: I agree with you, Dr. Hanauer.

CHAIRMAN HANAUER: Did I give you a chance to answer that, Arnie? Dr. Wald?

DR. WALD: No. I think practitioners, at least practitioners who enroll patients here, we think we know what diarrhea is even though we might argue about it. And it would clarify it to say diarrhea, even if you bring in some people who don't quite fulfill that criteria. so I think that's a more specific labeling that would be better for physicians.

CHAIRMANHANAUER: Dr. Ferry?

DR. FERRY: Yes, I believe I would include diarrhea. This would be for women with a predominantly diarrhea pattern.

DR. GELLER: I agree, but I'm more concerned about what we're going to say about constipation and the other lesser seen side effects.

CHAIRMAN HANAUER: So how would you label for contraindications, Dr. Wald?

DR. WALD: Constipation, constipation, and perhaps for now evidence of liver disease. You might just say that,

if you had someone who had liver disease, we don't know how that is going to play out and they might use that with a little bit of caution. I think that will be very few patients, though.

CHAIRMAN HANAUER: Although I presume from the clinical trials that patients with elevated liver enzymes were excluded from entry?

DR. MANGEL: Greater--

CHAIRMAN HANAUER: Greater than twice normal?

DR. MANGEL: Yes, greater than twice normal. If it would help the Committee at all, we do have Dr. Mitch Shiffman here, a hepatologist from MCV who has reviewed the entire LFT database, if that would help with any guidance, if you would have any questions for him.

CHAIRMAN HANAUER: I don't think we have any questions for him, frankly.

DR. MANGEL: Okay.

CHAIRMAN HANAUER: We thank him for being here. Good job.

DR. GELLER: I have a question.

CHAIRMAN HANAUER: Yes?

DR. GELLER: What about patients who have had previous colitis?

CHAIRMAN HANAUER: My purview is I'm not opposed to--you know, I don't think that that's a contraindication

hus far. I think that there are potential benefits in his, and certainly I think we'll look at it carefully. But I would probably exclude those who have had ischemic colitis, but I don't think it needs to be excluded for patients with inflammatory bowel disease.

DR. GELLER: I think we've heard today that ischemic colitis may not be diagnosed.

CHAIRMAN HANAUER: I'm not at all concerned that the data is showing chronic inflammatory bowel disease or colitis, and so I don't know that that should be a contraindication to this. For my constituency, who are patients with inflammatory bowel disease, I would not recommend contraindicating it in that population based on the data that we have now. That's my take on it.

Anyone else with contraindications besides constipation?

[No response.]

CHAIRMAN HANAUER: Caveats? Any additional comments on caveats? Dr. Wilson?

DR. WILSON: No. I was going to say it was constipation and liver disease. Is that right?

CHAIRMANHANAUER: And liver disease.

DR. WILSON: Yes.

CHAIRMAN HANAUER: Dr. Senior?

DR. SENIOR: Dr. Hanauer and distinguished

panelists, there really is no evidence that preexisting liver disease increases the risk of an idiosyncratic drug-induced liver injury, so that if you impose this restriction, you're going to have to do transaminases on everybody before you start the drug.

CHAIRMAN HANAUER: But it's very simple because from your standpoint the drug wasn't studying patients with abnormal liver enzymes.

DR. SENIOR: I understand.

CHAIRMAN HANAUER: So what you see is what you get.

DR. SENIOR: Right. I'm not sure that it should be restricted in the way that's being proposed because there's no evidence to support that.

CHAIRMAN HANAUER: How about if we say the drug has not been evaluated in patients with abnormal liver enzymes?

DR. SENIOR: A precaution should be made, and I hope that if you're going to be watching these patients, you will watch for that as well.

CHAIRMAN HANAUER: If we're watching which patients?

DR. SENIOR: You said you wanted to monitor the patients for colitis. Well, while you're doing that, you could maybe monitor them also for new elevations of ALT.

CHAIRMAN HANAUER: Well, that's a very different--one is a clinical decision, the other is putting a label that will be enforced for physicians to monitor liver enzymes starting this drug.

DR. SENIOR: Right, not necessarily in everybody, but perhaps in a cohort.

CHAIRMAN HANAUER: I'm personally satisfied--and I'll get the other members--that the drug has not been evaluated in patients with abnormal liver enzymes.

Other comments on that?

DR. WALD: I'd ask Dr. Shiffman if he would be concerned in someone with preexisting liver disease, not that it increases the risk, but should a complication arise, would they have a more severe reaction?

CHAIRMAN HANAUER: See, we got you in under the wire.

DR. SHIFFMAN: Yes, I finally made it.

CHAIRMAN HANAUER: You've come all this way.

DR. SHIFFMAN: I mean, Dr. Senior is exactly right. Patients with chronic liver disease do not have an increased risk for idiosyncratic drug reactions. However, if they have a severe idiosyncratic reaction and they have already established cirrhosis from their chronic liver disease, yes, they theoretically could be at risk for liver failure based upon that.

If you look at the data on liver transaminases, there were many patients in this cohort that did have mild elevations in liver transaminases or had elevations in transaminases even up to seven- to nine-fold normal that spontaneously resolved to normal during therapy. And that really speaks to the fact that there's very little inherent hepatotoxicity of this drug, and I think the recommendation proposed by Dr. Senior and the panel is actually reasonable that there's no evidence for--or that the drug has not been studied in patients with chronic liver disease and leave it at that. I don't think it's really necessary to say you need to monitor because there's really no evidence that it's there.

CHAIRMAN HANAUER: Okay. Any other caveats or monitoring? Dr. Ferry, anything that has been applied to--it has obviously not been approved yet for use in children, but any caveats you want to invoke?

DR. FERRY: No, I don't think so, actually. I mean, I think it needs to be studied in children. I would support it, but I wouldn't add anything. I don't see the liver issue as being any more than what the final comments were just a minute ago. I think that covers it. So, no, I don't see any other limitations related to pediatrics.

CHAIRMAN HANAUER: Dr. Geller?

DR. GELLER: No.

CHAIRMAN HANAUER: Dr. Wilson?

DR. WILSON: No.

CHAIRMAN HANAUER: It's finally a drug we don't need to study in women.

[Laughter.]

CHAIRMANHANAUER: Dr. Berardi?

DR. BERARDI: I read this material and I'm pretty comfortable with the lack of potential for drug interactions. But having seen drugs be approved and then months or years later see these incredible drug interactions, I guess that whole issue concerns me when there's one study in healthy volunteers with 15 patients and theophylline.

CHAIRMAN HANAUER: Any specific recommendations?

DR. BERARDI: Potential interactions with--I have to think about that.

CHAIRMAN HANAUER: Okay.

Dr. Wald, any caveats?

DR. WALD: No.

CHAIRMAN HANAUER: Okay, let me ask--yes?

DR. GELLER: I have one question. We talked about the drug being given for different durations than tested. We haven't talked about the drug being given to men. Once it's labeled, it can be given to men, true?

CHAIRMAN HANAUER: True.

DR. GELLER: Should we say here that it hasn't been tested in men?

CHAIRMAN HANAUER: Well, I think it has been tested in men to some degree, but there are also planned controlled trials that are in process in men.

DR. MANGEL: Yes. In our Phase II program, the efficacy was most clear in females. Considering that there has not been a new drug for IBS for decades, we wanted to focus on where we saw the efficacy. So that's why our initial Phase III program only addressed females. We actually just have recently started a large dose-ranging study in males to make sure that males are not being prematurely dismissed. So I think that answers Dr. Hanauer's question.

DR. GELLER: But it doesn't answer the question about labeling for now, does it?

CHAIRMAN HANAUER: I think it has. I mean, the labeling is going to be for women.

DR. GELLER: Thank you.

CHAIRMAN HANAUER: Dr. Senior?

DR. SENIOR: Would the learned panel comment on whether the drug should be used continuously, as studied for 12 weeks twice a day, or whether the patient should have some opportunity to adjust the regimen? They have proved the dose pretty well, but they haven't proved the regimen

that is optimal for management of the patient to avoid constipation.

CHAIRMAN HANAUER: Learned Dr. Wald?

DR. WALD: Well, I think that was the point I was alluding to before, is that you've established it within a fairly narrow therapeutic range for the purposes of demonstrating efficacy. But it may be that the patients will use it differently, particularly depending on cost and a whole host of things. So I would like to see those studies. I think there probably will be a middle range. I'm sure there will be people who might respond to lesser drugs. I'm sure there will be patients who are willing to take it episodically for episodic symptoms, and I would anticipate seeing it that way, although the initial labeling and indications will be for continuous use.

But as I mentioned before, I wold like to see the sponsor perform some of those studies as part of an open label process because I think this is a lifelong disease; it's going to recur. To take it daily, weekly, every month or every year after that is imposing a fairly significant burden. It would be nice if we knew that different approaches might be effective. Or perhaps the market will take care of that and physicians themselves will eventually take the lead in doing that. But it's worth considering.

CHAIRMAN HANAUER: I would probably leave as the

drug is indicated for the treatment of female patients with irritable bowel symptom diarrhea. I would probably add the caveat that in patients who haven't responded over the first month, there's no data that they are going to respond on a long-term basis.

And I think that just as Dr. Wald said, the reality is that modifications off of that are going to occur in practice according to individuals. As their diarrhea improves and their constipation comes on, the drug will be discontinued and restarted as they get diarrhea. That's going to be probably how it's used.

Dr. Wilson, any comments?

DR. WILSON: I guess one thing I was trying to remember from the data of onset of action--if there was efficacy prior to one week, that will probably be some important data because in some of the other drugs we've had people trying to use them episodically but they don't work for 24, 48, one week, or whatever. So it might be helpful for--you know, in the literature that will come about because if anyone ever presumes to think that they are going to tell the patients exactly how they are going to take a medication, they are dreaming.

CHAIRMAN HANAUER: Dr. Ferry, Dr. Geller, any other comments?

[No response.]

CHAIRMAN HANAUER: Can we address any other issues for the agency? We are here at your disposal.

DR. RACZKOWSKI: Well, there's still question 4(b)(ii), or did the panel already discuss that?

CHAIRMAN HANAUER: I thought we had discussed it.

Anything else?

[No response.]

CHAIRMAN HANAUER: Well, with that, first of all I would like to thank the agency for allowing us to be here, the panel for their time and effort in evaluating that, Joan Standaert for her constant supervision of this Committee, and also thank the sponsor for an excellent presentation and an innovative approach to a very difficult problem.

We thank you, and we'll close the meeting.

[Whereupon, at 3:47 p.m., the meeting of the Advisory Committee was adjourned.]

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CERTIFICATE

I, **VICTORIA RANUCCI,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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