beers, two glasses of wine, or one shot of hard liquor, and obviously, just as in the real world, there were people in these trials who did that. When you look at the alcohol users versus the non-users in the crossover trials, there really was no difference in adverse events.

Again, in the interaction trials, we got back up to the same dose of alcohol that that very first trial was, with an even higher dose of Uprima. The very first trial was 5 milligrams of Uprima, .6 grams per kilogram of alcohol. The 891 study was 6 milligrams of Uprima and .6 grams per kilogram of alcohol.

DR. AZZIZ: But that study was discontinued, was it not?

DR. FAGAN: No, no. The one that was discontinued was 5 milligrams and 6 grams per kilogram of alcohol.

DR. AZZIZ: The first one.

DR. FAGAN: Right. The final trial was 6 -- not 5, but 6 -- milligrams of Uprima and .6 grams per kilogram of alcohol. Same dose.

Again, we were making these people stand up repeatedly when the advice to these people is don't stand up in the clinical situation.

DR. AZZIZ: And what were the data for that study where they stood up and all this kind of stuff?

DR. FAGAN: That's coming.

But again, in their use at home, the alcohol users were no different.

Yes, when they had them together, everything was more common with the combination. There's no doubt about that. But again, remember, on the day that we were standing them up and sticking needles in them, that did not happen on the days when they got Uprima alone. And when you analyze that, you can see that that is a portion of the increase. Certainly a portion of the increase is related to the alcohol. Maybe we'll teach people not to drink when they take Uprima.

DR. AZZIZ: Yes, but they're supposed to be having sex.

DR. TIEFER: Thank you, Dr. Azziz.

DR. AZZIZ: They're going to be doing sort of up and down and things like that. So, I'm sorry.

(Laughter.)

DR. AZZIZ: This data is probably accurate for somebody who does drink four vodkas and takes Uprima.

DR. FAGAN: And stands up and down and gets needles stuck in them.

DR. AZZIZ: Or has sex, yes.

DR. TIEFER: And moves, tends to move.

DR. AZZIZ: Thank you. Thank you very much.

That's good.

Any other questions in this regard?

DR. LIPPERT: If you look at their purported instructions to patients at the end of the red book, the last page, what they're actually recommending is that Uprima can be taken following moderate alcohol ingestion. I guess if we're going to talk about labeling in the 4 milligram dose, I do have some concerns.

I think the most common drug that will be used with this is not Viagra, but is alcohol. Just as alcohol alters one's perception of what is moderate, once you start drinking, maybe that will change. Those who drive may not make good decisions. I just think that the labeling should show that there is a greater risk than they would suggest with alcohol ingestion.

DR. AZZIZ: Any other comments before we vote on question 2 and then elaborate on our labeling recommendations?

(No response.)

DR. AZZIZ: Let's go ahead and vote then. Again, the vote is do the data presented support an acceptable risk-benefit profile for the 2 milligram dose of Uprima, and then we'll elaborate.

DR. JACOBS: Jacobs, yes.

DR. O'LEARY: O'Leary, yes.

DR. DONATUCCI: Donatucci, yes.

DR. LIPPERT: Lippert, yes.

DR. CALIFF: I'm going to abstain until the 4 milligram dose discussion because I see the two as linked.

DR. AZZIZ: Azziz, yes.

DR. KOWEY: I'm going to do the same thing Rob did, abstain till we hear the 4 milligram discussion.

DR. D'AGOSTINO: D'Agostino, yes.

DR. AZZIZ: Dr. Graboys I think had to leave. So, we have one abstention.

MS. SCOTT: Scott. I'm going to abstain until I hear the 4 milligram.

DR. TIEFER: Tiefer, no.

DR. GREENE: Greene, yes.

DR. HANNO: Hanno. I'm going abstain till the 4 milligram.

DR. AZZIZ: I'm not sure that abstention was actually an option. This is a new thing. I'd rather have the committee members not go abstaining because we do need to give an answer, a yes or a no, for this.

DR. KOWEY: We will give you an answer.

DR. HANNO: If you're saying on its own --

DR. AZZIZ: On its own.

DR. HANNO: If we want to do the 4 milligram dose by itself, then I would probably say no on its own, if

we weren't considering any other dose.

DR. AZZIZ: I think we need to have a little clarification here. All of a sudden, this run of abstentions bothers me. Mary?

DR. MANN: I think we do wish for you to look at the two doses individually in part because, as we pointed out, the approvability of the 3 milligram dose is certainly contingent on each of these doses individually being found to be safe and effective. I can understand the committee wanting to have more discussion on the total risks and benefits of the 4 milligram dose perhaps before answering the 2, although we do ask, as you answer the 2 milligram dose, specifically just deal with the data relevant to that particular dose.

DR. KOWEY: Two comments, though, Mary. One is I don't know how in the hell we're going to approve a 3 milligram dose just off the bat because we have nothing to see for 3 milligrams.

DR. MANN: Absolutely, and we wish to clarify that. From our standpoint, both the 2 and 4 would have to have acceptable risk-benefit profiles. If they were both found to be acceptable, then the 3 would be implicitly approved based on the dose responsiveness noted and the dose proportionality noted.

DR. KOWEY: That's up to you, but if it were up

to me, I would say no because there's probably going to be an intermediate risk at 3 milligrams that I don't what that risk is. So, I couldn't approve a 3 milligram without knowing what that risk was, number one.

Number two, to approve a 2 milligram dose without a 4 milligram dose is a bit of absurdity because nobody really envisions too many people staying at 2 milligrams. You would never market 2 milligrams without having 4 milligrams.

DR. MANN: Right. I think part of the confusion is arising from the need for dose titration, which a lot of you are focusing on starting with 2 and working your way up to 4.

For this particular question, we ask that you solely address the data that you've seen with the 2 milligram dose alone and say do you think the risk-benefit profile for that data is acceptable or not. We understand that when you get to the 4 milligram dose, you're going to be talking about the dose titration aspects, as well as the 4 milligram data. Maybe that will make it clearer.

So, for this particular question, we are asking not the role of the 2 milligram dose as part of dose titration. We are asking you to address the safety and the efficacy data for the 2 milligram dose given as itself.

Does that help?

DR. AZZIZ: I want to remind the committee again we are simply advisory positions. The FDA makes their own administrative decisions after this. All we're here is to say yea or nay for the 2, yea or nay for the 4. If that appears to be yea for both, then maybe the 3 milligram dose, but that's not going to be up to us.

So, I'd like to ask, Marianne, do you want to revote? Like I said, you did not get people's understanding, and I'd like to go back.

DR. MANN: Yes, and I think if we all clarify, as we address this question, we are not talking about the approvability of the 2 milligram dose as part of a dose titration scheme up to 4. We are talking solely about the risk-benefit profile of the 2 milligram dose alone.

DR. AZZIZ: Questions?

DR. DONATUCCI: Yes. I just have a point of order. If we're going to revote this whole question, is it possible to go to question 3 first? This is just in order. Does it matter?

DR. MANN: It's up to the Chair. I think we're okay with that.

DR. AZZIZ: No. I want to stay with this question. We've just discussed the 2 milligram dose. Let's vote on the 2 milligram dose and move on. Thank you.

Dr. Jacobs, your vote.

DR. JACOBS: Yes.

DR. AZZIZ: Dr. O'Leary.

DR. O'LEARY: Yes.

DR. AZZIZ: Dr. Donatucci.

DR. DONATUCCI: Yes.

DR. LIPPERT: Lippert, yes.

DR. CALIFF: I guess if somebody wanted to bring forward a 2 milligram dose alone, I'd have to vote yes. Yes.

DR. AZZIZ: Azziz, yes.

DR. KOWEY: Yes.

DR. D'AGOSTINO: D'Agostino, yes.

MS. SCOTT: Scott, yes.

DR. TIEFER: Tiefer, no.

DR. GREENE: Greene, yes.

DR. HANNO: Hanno, no.

DR. AZZIZ: Thank you.

The yeas have them. Please let's elaborate and give some labeling recommendations and other concerns that we have to the agency so they can utilize this later on. Any comments for starters?

DR. JACOBS: It's unproven for use in people with no erectile function, MS, spinal cord injury, and Parkinson's disease, and it should be used with minimal alcohol intake.

DR. AZZIZ: I'd like to stress in the labeling I think it's minimizing the interaction with alcohol in both the patient instructions and the potential labeling. It has to be very clear that this should be no more than one drink or two drinks. Moderate drinking for my patients often means a six-pack a night, only a six-pack.

(Laughter.)

DR. AZZIZ: So, that is of no help. That has to be very clear, and potentially in a block in the label, in a separate block.

Dr. Donatucci.

DR. DONATUCCI: I'd just like to say I think it's also important to, in block labels, mention the syncopal aspects of the drug. It's not certainly the only drug we use for this condition that does that. Already when we treat patients with other agents, we have to discuss those questions with the patient. But I think it's important that that be emphasized and physician education.

DR. MANN: Can I just clarify? When you say putting this in a separate block, are you implying a boxed warning, a warning with a box around it? I just wanted to get clarity there.

DR. AZZIZ: Yes. I would prefer a warning with a box because very often neither prescribing physicians nor patients ever look at this, and it's only the boxes that

they look at.

DR. MANN: So, for both alcohol and I heard a recommendation for syncopal events.

DR. AZZIZ: That's our recommendation. Correct.

Dr. Greene.

DR. GREENE: I was going to, along those lines, suggest, given some of the vignettes, in that boxed label, with respect to syncope specifically, saying something about driving a car or operating machinery, that sort of thing.

DR. AZZIZ: I thought you meant the descriptions of the patients.

(Laughter.)

DR. AZZIZ: Dr. Califf.

DR. CALIFF: I think this will be even more pertinent if the 4 milligram dose is approvable. Several drugs have recently been approved that have required a patient leaflet which goes beyond the label. Typically I find that less than 1 percent of physicians have seen a label in the last year. So, I think it's highly unlikely that putting anything in the label is going to make any difference. In fact, the cisapride experience pointed that out. Even writing letters to physicians is not going to change the information that's passed on to patients. So,

I'd like to see it go a step beyond, as we'll get into in the 4 milligram discussions.

This drug is clearly going to kill some people and it's going to be most likely be people who have severe coronary disease and have hypotension and syncope. I think it's really incumbent upon us to try to figure out what to do about the risk that's going to be unleashed at any dose.

DR. KOWEY: I guess I'm the token EP person who takes care of syncope day in and day out. For those people on the committee that don't see a lot of patients with syncope, it's a devastating disease. It's an absolutely devastating disease. We haven't gotten to the 4 milligram discussion. I voted yes for the 2 milligrams because we're dealing with a relatively low incidence. The incidence is much higher at 4 milligrams, and that's why I'm sort of reserving a lot of my comments, as Rob just said, for the subsequent discussion of 4 milligrams. Because I'm sitting here silently doesn't mean that I'm taking this lightly.

Rob is right. There will be some people who will probably lose their lives because they'll pass out at the top of a flight of stairs or they'll be operating a car at the time that it happens. So, it's a very, very serious adverse event.

I also want to just say that having known that there was syncope present in a substantial portion of this

patient population, I'm flabbergasted that there was no attempt in the clinical trials to define hypotension. I mean, how could we have an incidence of syncope this high and then let the investigators tell you when they had hypotension? I think that's close to being irresponsible. I think that there should have been protocol-defined endpoints to define serious hypotension when you have a drug that causes syncope because of a vasodilator response. I'm really unhappy about this because we're now left with this free-floating anxiety about hypotension without being able to really nail down the number.

DR. AZZIZ: If you can respond please, make it brief --

DR. FAGAN: I showed you a trial with 450 patients that had blood pressures measured at frequent intervals.

DR. KOWEY: No, that's what I said. Let me clarify exactly what I said. There clearly were patients in your clinical trials who had SAEs that were hypotension. When you have a drug that causes syncope, prospectively you can't not define what a serious adverse event is for hypotension. You can't say to the investigator you figure it out, tell me when you think somebody got hypotensive. You need to tell the investigator, when the blood pressure hits this number, you got to register that as an SAE so we

can quantitate it.

Clearly some of the cases that Mark presented that were not coded as syncope were coded as hypotension were as serious as the syncope. I think Mark said that during his presentation. So, we're going to have a very difficult time now with this because we don't have that quantification.

That's different than measuring blood pressure. The vast majority of people in your studies didn't get hypotensive. I agree with you. You're right, but there were some people who became not only a little hypotensive, they became very hypotensive and some became syncopal, and it's a continuum. We don't know those numbers because they weren't prospectively defined, and it's a problem for us.

DR. FAGAN: We have it in 450 patients and most of the doses of the 75,000 doses were taken at home. So, you can't really get blood pressures there.

DR. AZZIZ: Thank you.

DR. RACZKOWSKI: Dr. Azziz?

DR. AZZIZ: Yes.

DR. RACZKOWSKI: I just want to follow up a little bit on what Dr. Califf said, and I'm interested in getting some additional advice from the committee on this. We've had a number of drugs recently withdrawn from the market despite labeling changes and despite black boxes.

Dr. Califf mentioned cisapride. There has also been Durac. There's been Posicor. I wonder what recommendations, that you could consider in your deliberations, the committee would have in terms of trying to ensure that labeling recommendations are actually followed.

DR. AZZIZ: Are actually followed? What do you mean, they're actually followed?

DR. RACZKOWSKI: Well, if we put a black box in saying that you should use minimal alcohol, how do we ensure that that will have an actual impact on patient care?

DR. AZZIZ: Thank you. When you said actually followed, I thought the sponsor printing it. Okay.

I think we will because that involves education and other programs, and we'll do that.

Dr. Califf.

DR. CALIFF: I was just going to say I don't think any of us actually know empirically now what does work. The sponsors obviously will write down what you tell them to write down. That's almost 100 percent. Physicians reading what's written down or following the instructions -- there's actually no empirical base of research that I know that tells us what does work. But at least I'm enamored now with patient activation as a concept, requiring that when the thing is dispensed, that the

patient actually get a readable document that says, here's what you need to be worried about. It ought to at least have some impact. I'm not sure it will, but it might.

DR. AZZIZ: Dr. O'Leary.

DR. O'LEARY: I'm just trying to think of other instances of this in urology. We know that when Viagra was approved, it was very clear that it was contraindicated in association with nitrates. That was very clear. I think every urologist knew it, and we told patients that if they took Viagra with nitrates, they would die. And that was basically what I told patients. Now, that didn't stop some people from doing it, and I had a number of patients who lied to me about whether or not they were on nitrates. And then I found out subsequently from their pharmacist who called me and said you just wrote a prescription for someone who's on nitrates. So, I don't think we can prevent patients from doing what they will do.

But I think proper labeling and education of the physicians who are prescribing it -- I don't know. Let me ask some of the other urologists here who routinely write for this drug.

DR. LIPPERT: When Viagra first came out, I was very disappointed that there was no patient handout. I had to write my own. There was one eventually that came out. I'm pleased there actually is a template here for a patient

handout. Whether or not it will actually be available at the time the drug is approved, I don't know. With Viagra, everybody gets a handout, everybody gets a lecture. I think this is got to be the same for this drug.

DR. GREENE: Ricardo, if I may.

DR. AZZIZ: Yes.

DR. GREENE: There are two models out there for drugs that have a very high risk associated with their use where the companies have gone to extreme measures to advise potential users of those risks, and those are Accutane and thalidomide. Both of those drugs are prescribable. They're prescribable, in the case of Accutane, by any physician. In the case of thalidomide, there is a very extensive program of not only patient education, but also the doctors who prescribe it have to register with the company, and the pharmacists who dispense it have to register with the company. Now, that is a model that would be very, very difficult to implement for many drugs, but at least there are those two models out there, the Accutane model and the thalidomide model, where drugs have substantial risks associated with their use in the wrong setting, that the companies have been fairly successful in preventing rampant misuse, let's put it that way.

DR. AZZIZ: Before we go on to try to describe some of these things, which I think all of us will have

ideas for the FDA, I'd like just to remind you that we do need to have the third question answered because, obviously, that will really determine where we're going. So, let's move on to number 3, and then following that, we can elaborate as much as we'd like because that is what we're paid highly to be here to do.

(Laughter.)

DR. AZZIZ: So, do the data presented support an acceptable risk-benefit profile for the 4 milligram dose of Uprima? That is the question on the table now.

Comments about specifically this before we vote. Dr. Califf.

DR. CALIFF: I guess my opening feeling is that the studies have met the specific criteria that I would regard as being acceptable. That is there's a clinical benefit defined in a tangible way that we can believe in. It's highly statistically significant, so there is a benefit.

There's also a risk. Peter I think has more eloquently than I could described the frustration over the difference between an average drop in blood pressure, for example, an idiosyncratic clinical events, which really do need to be prespecified and recorded as part of phase III clinical trials. We're just stuck with that and I don't think we can do much about it.

But I think given the patient who's not drinking and not on a bunch of cardiac meds and doesn't have three vessel disease and is not going to drive a car for the next hour or so, I would say this meets my criteria.

DR. AZZIZ: Any other comments before we vote? Dr. Greene.

DR. GREENE: There are two questions that I consider in voting on this. One is what is the disease that we're treating. Although as important as this is, it's not cancer. This is not the cure for cancer, and this may be very important for some people, but it's not cancer. That is my first thought.

The second thought is that this is a medication which is going to be given, if you will, or taken at home, not directly or immediately under the supervision of a physician. This isn't like a medication that's administered to an in-patient in the hospital. So, when I think about the risk-benefit ratio for a cancer chemotherapeutic agent, you're treating a life-threatening disease and it's being administered in a hospital setting, let's say, under direct physician supervision.

So, I think those are two issues that I think about as I think about voting on this question. The ratio that we would demand for safety I think is different for

this than it would be, let's say, for a cancer chemotherapeutic agent.

DR. AZZIZ: Dr. Hanno?

DR. HANNO: I think that, as Dr. Jacobs has pointed out a few times, there should be and the indications should reflect the population that the drug was studied in.

I think that the 4 milligram dose does seem to have some efficacy.

I'm a little worried about the alcohol. When you give people permission to drink alcohol, sometimes they're not going to stop on their own or they're going to lose sight of what they're drinking. That seems to be a potential risk factor, and I'm wondering whether that needs to be addressed in the label and perhaps alcohol should be something that's contraindicated, or at least it should be stated that it's a known risk factor for severe side effects and not give somebody a safe level of alcohol to drink, but rather try and stop people from drinking alcohol with this.

Then I don't know whether we should consider a warning on a label about eating prior to taking this drug. In some cases it might make it less palatable, but I think that it's something to consider given the data on the nausea.

DR. AZZIZ: Dr. O'Leary?

DR. O'LEARY: I agree with Dr. Hanno. Patients are, I think, pretty used to asking, can I take this drug with alcohol, and I'm not sure why often they ask that. But I would favor the label saying this drug should not be taken with alcohol, just the way a whole bunch of other drugs that we commonly prescribe for people are labeled. Then that would take away the concern to some degree. I mean, people are still going to drink and take it anyway, but if the label clearly said, it's not recommended that you have any alcohol when you're taking this drug.

DR. AZZIZ: Dr. Jacobs.

DR. JACOBS: The acceptable risk:benefit profile. The risk is about what many other drugs out there are. For hypertension, it's very similar in its risk. Its benefit profile may be underestimated because any urologist has guys in the office when you say you can't have Viagra, you'll have a heart attack and die, they'll just look back at you and say, that's all right. I don't mind. Give me the pill. And that's very common. Whereas, maybe everybody in this room doesn't value erections as greatly as some of these patients, there's a large number of patients out there where this is their raison d'etre, and that's the only reason they're on earth.

DR. AZZIZ: Any other comments before we vote

on the risk-benefit ratio for the 4 milligram dose?

(No response.)

DR. AZZIZ: Let's go ahead and go around the table then. Again, do the data presented support an acceptable risk-benefit profile for the 4 milligram dose of Uprima?

Dr. Jacobs.

DR. JACOBS: Yes.

DR. O'LEARY: O'Leary, yes.

DR. DONATUCCI: Donatucci, yes.

DR. LIPPERT: Lippert, yes.

DR. CALIFF: Califf, yes.

DR. AZZIZ: Azziz, yes.

DR. KOWEY: Kowey, yes.

DR. D'AGOSTINO: D'Agostino, yes.

MS. SCOTT: Scott, no.

DR. TIEFER: Tiefer, no.

DR. GREENE: Greene, no.

DR. HANNO: Hanno, yes.

DR. AZZIZ: Thank you.

Now we need to elaborate and give our recommendations to the FDA.

DR. KOWEY: As Dr. Azziz has said several times today, our role is as an advisor. So, nothing that we tell you is binding obviously. If you came back and told me

several months from now that you decided not to approve this drug, it would not break my heart because I think there are two ways to handle this kind of a problem. One way is to not approve the drug. Period. And the other way is to approve it and then label the hell out of it. I voted yes with the proviso that you understand that there's got to be a tremendous amount of work done on labeling for this drug.

I favor a black box warning in bold letters that says, that if you take this drug, you may pass out and if you pass out, you may injure yourself and you may injure yourself severely.

I also very, very adamantly favor a patient package insert which is carefully constructed along the lines of what was done for dofetalide and also for Betapace AF, the last two drugs from the Cardio-Renal Advisory Committee that I know about that I was involved with that have detailed instructions given to the patient about what drugs to avoid, what situations to avoid, and how to maximize the safety of the drug, and what kinds of things they can get into trouble with, drug interactions, et cetera.

I don't want anybody to interpret that this is an approval that is sort of like "see you later." This is an approval with the stipulation that there's a tremendous

amount of work to do because, as I said earlier, the complications that have been seen with this drug are frightening complications. And it's also been said by people at this end of the table we're not treating cancer.

So, as important a drug as it is -- and I said yes because I was listening to these guys who take care of these patients who would like to see this drug available. And I agree that they're a desperate lot of patients and they do need to have that drug, and I'd like to see it on the market. That's why I voted yes. But don't take that to mean that I don't have grave concerns about the safety of this drug, and if it's not communicated properly to the physicians, what's going to happen is you're going to run into the same withdrawal problems that you had with other drugs that somebody else mentioned earlier. So, I feel very strongly about that.

DR. AZZIZ: Dr. Tiefer.

DR. TIEFER: I just wanted to say a word about the secondary effects on the partner. This is one reason I voted no because when I think of a sexual problem, I know this is not the typical medical model way, but I think of it as a couple's problem not a person's problem. In my experience, the drugs, the treatments that the patient individually chooses with his physician have serious ramifications on the partner's well-being, for the good

sometimes, for the not so good other times.

When I heard what Dr. Jacobs said that the guy comes in and says, this is my raison d'etre and I'll die if you don't give it to me, I know that the partner is thinking, having talked to many of these partners, at that very moment. She's thinking, God, I hope the doctor doesn't give him anything because the last thing in the world I need is to worry about him. In addition to him taking his this, that, and the other medication, and going for these tests and so on and so forth, now he's going to be taking something else which has a little black boxes, and I, the wife, am just really frightened about this. It's not to say that she doesn't want to have sex and want her husband to have the pleasure of sex. But this stressor -- she's more up front about that.

So, I just feel that we need to take into account the consequences of this on the other people, the less visible people who are involved with this, and that it's not a matter of such great urgency that we need to approve a drug that's going to have lots of black boxes, which for the wives are just terrifying.

DR. AZZIZ: Thank you.

Dr. Lippert?

DR. LIPPERT: Again, I'm repeating myself, but when Viagra came out, there was no patient handout. I had

to write my own. I'm a urologist, but there were community primary care physicians who were just calling my office begging me for a copy. My chairman said, no way, you'll be legally responsible. I really don't think this drug should come out without an available handout for patients that's available when the drug comes out to primary care physicians, to all physicians. I feel strongly about that.

DR. AZZIZ: Dr. Califf?

DR. CALIFF: This is also somewhat repetitive, but I think just to get down to what I think the most critical issue is, if we look at the recent messes that we've had, what tends to happen is that the real bad things happen to people who have a confluence of multiple risk factors at the same time, and the people that are going to die with this drug are people on multiple antihypertensives or people with severe coronary disease who are perhaps unlucky.

But at least I would argue that the label ought to be very restrictive to start with and then the company ought to have a chance to work sort of backwards into those populations in a little bit more detail because I'm not satisfied with the studies yet related to alcohol, for example, or to multiple antihypertensives at the same time or to nitrates.

I'd like to see some pretty explicit material

that would be given to patients. Admittedly a lot of them wouldn't pay attention to it or they might go ahead, but then at least they would do so under informed conditions. I don't think the fact that some people don't have good common sense should disallow others who would use the instructions the opportunity to have access to the treatment.

DR. AZZIZ: Dr. Hanno.

DR. HANNO: I would agree that the label, if this drug is approved, needs to be extremely restrictive, and later as time goes on and more studies are done, if it turns out to not merit that, then that's fine. It could be changed. I think it's going to be used by a lot of non-urologists, primarily family care, primary care people, and the word has to get out that this is not a benign drug, that it has significant safety concerns. I'm sort of guiding what I'm saying with Dr. Kowey, what he was saying in terms of the danger that's implicit in approving the drug.

DR. AZZIZ: Julia?

MS. SCOTT: Yes. I remain very concerned that the population of African Americans is so low in this study. I think we all know that this is a population that has the highest risk of those diseases, diabetes and hypertension and cardiovascular disease. So, I'm concerned

that we don't know enough about how this drug might act in African Americans. We also know they have the least access to health care. So, some of these incidents that have been described as kind of minor could actually be very major for that population.

I'm also concerned that if this drug does get approved, that there be a registry or something that keeps track of people so that we can track some of these results because it would be a shame to wait until we start having deaths. I'm very concerned about the side effects, especially in the higher than the 2 milligram. Actually I'm concerned about the 2 milligram too, but I think they're more pronounced in the 4 milligram.

So, I would hope that if the FDA approves this drug, that there is a restricted label, that there is some kind of physician training, because again it's not going to be just urologists who have a better feel for the appropriateness of this, as well as the patient insert, that it clearly state the problems related to alcohol intake as have been described earlier.

DR. LIPPERT: Excuse me. A patient insert won't work if it comes in the box because I don't have the box in my office. So, there actually has to be a patient handout separate from an insert because I'm not a pharmacist.

DR. AZZIZ: That is one thing. I have a question for Dr. Mann because before we get into recommending things such as educational programs and brochures and so on, how much really can we recommend? We can do that, but if it has no impact.

DR. RACZKOWSKI: From what I've heard, there are two ways that it could be ensured that patients get the information about the labeling. One is by recommending a unit-of-dose distribution of the drug, which means that whenever the drug is distributed a package insert goes along with it to the patient. Another option is to use the patient package insert or a med guide, which are different things, and to have them not only as part of the formal labeling of the product, but also distributed by pharmacists to patients when they fill prescriptions.

DR. AZZIZ: But you can't regulate physician education, can you?

DR. RACZKOWSKI: No. As a condition for approval, we could demand educational programs, yes.

DR. AZZIZ: Very well. That's what I wanted to make sure before we went off into this tangent.

Comments? Dr. Mann.

DR. MANN: We heard a fair number of specific comments about the alcohol interaction, anywhere from a contraindication to a black box warning being suggested.

We also heard your strong comments about warning at least in a black box fashion about syncopal events.

In terms of the nitrate interaction, I would like the panel, if they could, to discuss a little bit more specifically where in the label they think that information might go. I don't mean for you to fully understand labeling, but in general, labeling things range anywhere from a contraindication statement, which is very strong, meaning absolutely never give this drug with nitrates, to the potential for another black box warning in this regard, or a warning all the way down to a precaution.

The current label proposed by the sponsor, on page 178 of our red binder that we've presented to you, the first paragraph under Precautions precautions people against concomitant nitrate use. I'd just like the panel, if they could, to discuss if they feel that is adequate or if they have a different opinion on how to warn about nitrate interactions.

DR. AZZIZ: I'd like the two urologists on the panel to begin. They've been very quiet. I mean the two cardiologists have been very quiet. So, perhaps if could get your feedback initially. Dr. Califf.

DR. CALIFF: My initial feeling would be that it should be a contraindication for the time being. There was a nitrate study. I'm having trouble remembering all

the details. Maybe we should look at that data one more time.

DR. KOWEY: My recollection was that for the short-acting drugs, the means were really not any different than for the long-acting. There was a statistical difference, but it didn't look all that clinically important.

DR. MANN: That's correct.

DR. KOWEY: But there were, as you pointed out, a number of outliers and exceptions.

I agree with Rob. I think it probably ought to be a contraindication until this is perhaps ferreted out a little bit better and there's more experience. I don't really think that that should be a major problem clinically. I don't see why that would be a problem.

DR. CALIFF: The combination of syncope and nitrates in any form is pretty scary because it's not uncommon to see syncope caused by nitrates.

DR. KOWEY: Well, let me just remind everybody that when we do tilt table testing, if we tilt somebody and they don't go out, and they don't have syncope on a tilt table, one of the ways of provoking it is by giving them nitroglycerin, so for cardioneurogenic syncope, vasovagal syncope, which is what this is. So, there's a perfect rationale to say since this drug causes vasovagal syncope,

that you shouldn't be taking nitrates if you're going to take this drug. So, I don't have any problem at all with the contraindication statement.

DR. AZZIZ: Again, we can black box it or contraindicate it. Any other comments, please?

DR. JACOBS: The data they presented on nitrates on this sure didn't show much of a blood pressure drop with the 5 milligram Uprima dose with nitrates. Nothing as dramatic as the sildenafil drug that's already out there. This is one of the benefits of this drug presumably.

DR. CALIFF: Well, here's the rub. It's just like what Peter was talking about with regard to syncope and hypotension in general. A mean difference in blood pressure is not the same as event rates, which require fairly large studies to detect. So, if you have an occasional patient, 1 or 2 out of 100, where there's going to be hypotension due to the nitrates per se and you add on top of that, it could really be a mess.

DR. JACOBS: Why don't you just say no sex for nitrate patients then? I mean, sex probably lowers your blood pressure or raises it one way or the other.

DR. CALIFF: Well, there is an alternative, which is to do larger studies that really measure event rates and not just mean blood pressures in a small

population. That is quite a reasonable alternative. I think there are a few million people who might end up taking this drug.

DR. O'LEARY: That's I think what Dr. Graboys had suggested before he left, or at least that was my interpretation.

Let me just ask you cardiologists a question. I'm puzzled. I understand what nitrates and sildenafil do in combination, and that's a direct drug effect. But you're not suggesting that this drug has some direct effect with nitrates. It's simply that the drugs in combination --

DR. KOWEY: No. I'm suggesting that there is a central mechanism for cardioneurogenic syncope. We know that. That's been well worked out. We know that nitrates do something centrally -- centrally, not necessarily on the periphery -- which potentiates the tendency to a vasovagal episode such that, as I said, in somebody that has a tilt table test, if they don't become syncopal with the tilt and they've had spontaneous neurocardiogenic syncope, you give them nitroglycerin and retilt them, and you see the neurocardiogenic response. So, it's not just an additive effect on blood pressure. There is a specific trigger that nitroglycerins seem to cause to provoke a vasovagal reaction.

And that's what this is. This is not the same thing as Viagra. I don't think this is the same mechanism of hypotension.

DR. O'LEARY: We know it's not.

DR. KOWEY: Viagra is a vasodilator. This is not acting by a vasodilatory mechanism. It's acting by a mechanism which provokes a vasovagal response. And nitroglycerin potentiates that synergistic effect. That's why it's perfectly reasonable in my mind until we have more information to say no nitrates.

DR. AZZIZ: Very well.

Any other comments about the nitrate issue? Marianne.

DR. MANN: Thank you for those comments and if there are any others, please let me know.

DR. AZZIZ: Just maybe a couple more.

DR. MANN: Actually I had one other issue for the panel to address. Many of the syncopal events that were noted in the sponsor's application occurred with the first dose of study drug or with an increase in study drug dosage and were given in the physician's office to the patients.

Another potential labeling recommendation that we could take under consideration would be the requirement for all initial doses to be given in a physician's office

under physician supervision. I'd like the panel to address that potential idea for labeling as well, if you don't mind. Thanks.

DR. AZZIZ: Dr. O'Leary?

DR. O'LEARY: We have experience with this with another already approved drug, and that's intraurethral prostaglandin. When that was first approved, it was recommended -- I'm not sure it was part of the labeling, but it was recommended that patients be dosed in the office. I don't routinely and I don't think most urologists routinely do that anymore, aside from the fact that we don't prescribe very much anymore because the efficacy is not great.

I can see some potential problems in doing that, simply that the volume of patients that are likely to come forward to request this may be fairly substantial.

DR. MANN: Thank you for that comment. Actually for the intraurethral injections, they are recommended in labeling to be done in the physician's office. Perhaps this is one lesson learned as to how far we can go with labeling recommendations to assure patient safety, to assure that our directions are truly followed in real life, and that was a very relevant comment you made in that regard.

DR. DONATUCCI: Can I make a comment?

There is a second part, of course. While we stopped doing it in the office, every time we give the patient a prescription for that, they are carefully instructed about the possibility of syncope and what to do. But I would hazard to say probably that particular product that we're discussing right now, the transurethral alprostadil, is a product used primarily by urologists who are familiar with that.

DR. AZZIZ: Dr. Lippert?

DR. LIPPERT: I just want to say I'm still following the recommendations, and I still check blood pressures when I give the first dose of Muse in the office.

DR. O'LEARY: Maybe you could talk to that other agency --

DR. AZZIZ: To come and look at Dr. O'Leary's --

(Laughter.)

DR. O'LEARY: No, no. I'm suggesting one of the reasons why we stopped titrating in the office is because that other agency up the road, the Health Care Financing Administration, stopped paying for it.

DR. AZZIZ: It's a very good point.

I just have a couple comments. I'm not the urologist. But a recommendation to have those doses in the office doesn't necessarily guarantee very much. All the

crashing and burning we saw were in physician's offices. In a busy practice, I don't know what it guarantees other than somebody can code the person faster perhaps, maybe.

The second thing is we do need to come back to the issue of education. Dr. Lippert says stuff in the box isn't read, and so the company, if they're going to market this, needs to produce a brochure both for the patient and for the partner because I think it's an important issue. This is what you need to expect from your partner. And given to the patients. They need to be in the physician's office, given to the patients, a colorful brochure. Otherwise, it just isn't going to get read. Whether this is signed for when they get the drug or something of that nature, that's perfectly fine.

DR. TIEFER: One of the other things that's more popular over time are videos that are being given to patients along with drugs by urologists. This has been quite common over the last few years. You have the opportunity to put a little sex education in the video along with the drug education.

DR. AZZIZ: Then we'd have all the 15-year-old boys standing for the video.

(Laughter.)

DR. TIEFER: No. Sex education is not XXX movies, unfortunately, Dr. Azziz.

(Laughter.)

DR. AZZIZ: Dr. Greene.

DR. GREENE: Two comments. One is that with respect to that, I'm not sure how long would you advise the patient remain in the doctor's office? Because some of the adverse events literally were on the way home from the doctor's office after what appeared to be an uneventful first administration. So, I don't know. How long do you tell the patient to stay in the doctor's office? It might be safer to tell the patient to go home and taking it lying down in bed. So, I'm not sure.

One other last comment from the voice of doom. In other medications that have been removed from the market because of adverse events -- such things as cisapride was mentioned, fen/phen, recently troglitazone -- at least in those occasions, the problems with the medications were not obvious and did not occur in the studies of the drugs initially. As Dr. Califf mentioned, showing a modest decrease on average is not the same as finding out what percentage of people will have a very dramatic fall in their blood pressure. Studying only 3,000 patients is not going to tell you about a lethal problem in 1 in every 10,000 patients. So, that's my last concern from the voice of doom.

DR. KOWEY: This problem of safety, obviously,

in the cardiovascular end of things has become so important lately. We've thought a lot about sample sizes and detection thresholds and where you get enough people in the study to really make yourself sure. Unfortunately, I guess at the end of the day, there's always a leap of faith when a drug is approved it's going to be used in about 100 times more people tomorrow than it was used in all the clinical trials. So, I don't know if there's any way to really do that.

I just want to add my comment about office initiation. I don't think it's necessary. In fact, I agree completely. I think it's probably safer, for this particular kind of a drug, if you do what Dr. Donatucci suggested, tell the patient what to do when they get home. It's probably much, much more effective.

DR. O'LEARY: Dr. Azziz?

DR. AZZIZ: Dr. O'Leary.

DR. O'LEARY: One other comment. I don't want to be a voice of doom necessarily, but this drug will be given in a population of men who have a significant risk of sudden death to begin with just because of their age. So, let's be real clear that some of the patients who take this drug are going to die. Now, that's the reality. Now, whether that's due to the drug or not is something different. From what I've seen, it doesn't suggest to me

that there's anything that this drug will do to directly contribute to death. Is that fair? I just want to make sure that we're all clear about that. Some of these men are going to die.

MS. SCOTT: Well, we're all going to die.

DR. O'LEARY: Right.

DR. KOWEY: The fact that there weren't any deaths in the program is good. That's good. That's a very good thing, in fact, in 3,000 patients that got the drug. There had to be some people in there that had pretty bad vascular disease. Had to be. Nobody died and nobody, in fact, had a cardiac arrest and was resuscitated. Nobody had symptoms that sounded like VT. So, all that's good. But it still doesn't answer the ultimate question of where your detection threshold is and what you'll tolerate.

DR. AZZIZ: I think what you're hearing, Marianne, is that we'd like some post-marketing surveillance data, whatever you all think is necessary, because while the committee seems to have recommended this, having been on a number of these, the committee is pretty uncomfortable with the safety profile. We're going to need more data on nitrates and heart disease and diabetics and alcoholics and so on and so forth that we don't have the data now sufficiently.

DR. MANN: Would such data in a wider

population of patients studied be more useful to you pre-marketing or post-marketing? Could you comment on that?

DR. AZZIZ: That's a tricky question. Often you will not get the experience with the patients unless you actually market the drug, as we found out with lots of drugs. You can never market in my opinion a drug that has no side effects. It just doesn't exist. If you take a larger number of patients, eventually somebody is going to die. So, that's my bias.

Dr. Califf?

DR. CALIFF: I finally found a handout on the nitrate studies. There were 20 on short-acting nitrates and 20 patients on long-acting nitrates. To me, this is totally inadequate, completely and utterly inadequate. And it's true that if you don't study things, you won't see them. So, in terms of pre-marketing data, I don't think it's impossible to get pre-marketing data. We just need studies that are done in the patient populations in whom the drug is going to be used after it gets on the market, probably with larger numbers. But that's not going to change what happened today.

The problem I think with the post-marketing surveillance issue is it's pretty hard to come up with a non-randomized, post-marketing scheme that's going to help you in this situation because, as Dr. O'Leary pointed out,

a lot of these people are going to die in proximity to taking the drug, totally not due to the drug but due to the underlying disease. So, in absence of randomization, I don't know how you draw inferences from post-marketing rates.

DR. AZZIZ: In answer to your question about pre- and post-marketing data, as Dr. Califf just brought up, the alcohol issue has been looked at fairly well in some studies, not perfectly, but fairly well. The nitrate studies are basically insufficient and inadequate, and unless we can simply contraindicate nitrates, period, anything else that needs to be brought up needs to be restudied before this drug is marketed.

Julia?

MS. SCOTT: Also, I think the pre-marketing is necessary for African Americans. I just think the number is just too low and too many studies have shown differences among African Americans in terms of side effects and the like. So, I do think you need to study that.

DR. AZZIZ: Any further comments?

DR. TIEFER: I just want to say one more point about sublingual training. Nobody has mentioned this.

DR. AZZIZ: Training.

DR. TIEFER: I just thought it was interesting. In their initial trials, they discovered that if they

didn't offer the patients some training in the use of a sublingual drug, that the drug wasn't absorbed properly, wasn't utilized properly. So, somewhere along the line, this has to be part of this patient information.

DR. AZZIZ: Very good.

Any other comments?

(No response.)

DR. AZZIZ: I think Dr. Mann has some closing comments. Correct?

DR. MANN: Yes, I do. I just want to thank you all for your participation today.

In addition, I want to draw attention to two committee members who have served us for many years and done extremely well. That is Julia Scott, our patient advocate, and our Chair himself, Dr. Ricardo Azziz. I want to assure you both that we very much valued your input and expertise these past few years on our advisory panel. We do not throw your recommendations into the closet.

(Laughter.)

DR. MANN: We actually consider them very highly, and although we do not pay you very much, we know, our heartfelt thanks hopefully will suffice somewhat.

We also have a small plaque to give you both before you leave, and we just want to give you a round of applause for all of your participation.

(Applause.)

DR. AZZIZ: Thank you very much and thanks to everybody for staying long.

(Whereupon, at 3:55 p.m., the subcommittee was adjourned.)