are clear indications now for anticoagulation.

CHAIRMAN PACKER: Okay. Therefore no mention? Anyone disagree?

DR. THADANI: I think all patients should be anticoagulated who are--

CHAIRMAN PACKER: That is not the question. The question is should the labeling say so? We said not to say it in dofetilide. So the same here as for dofetilide? Tom? That is fine. Okay. Last two questions, should a -- what program should be instituted to determine what fraction of patients are receiving sotalol in accordance with the dosing regimen that would be recommended? This is a requirement for a formal comprehensive post-marketing surveillance program. Something like that was discussed with dofetilide. It wasn't entirely clarified. Do you think that kind of surveillance is important for this drug? JoAnn?

DR. LINDENFELD: This is a hard one. I think that the things that every physician should know are obviously the calculated creatinine clearance and the QT interval. And that is what everybody should

know with dofetilide too, in addition to some other things. So I think probably they should be required.

DR. FENICHEL: Well, that is not the question unfortunately, because that is easy. I mean, the question that you are answering is --

CHAIRMAN PACKER: The question is what is it.

DR. FENICHEL: Well, the question that JoAnn was answering was how should the drug be given. Well, of course, that is what you have been answering for much of the day. The question that we are asking here, and it is the same question that came up with dofetilide, is there something that should be part of the approval package that guarantees -- or guarantee may be too strong -- that makes it more likely that this advice that will be in the labeling is in fact being heeded. And the extreme example that is given in the question is that used with Clozaril, where the problem in that case is a matter of getting repeated CBC's to look for neutropenia, which is caused by that drug in something like 1 percent of the patients. And what is done there is that patients may not obtain the

drug without demonstrating that they have shown up and got their blood drawn. Now that is about the most radical case that I know about in terms of making sure that the drug is being given right. Actually, there is another one that is in progress for the reappearance for some age-related and other indications for thalidomide, where you really want to make sure that people are getting the drug right. So that was the question that was raised with dofetilide. Not how do you give it, but rather what should be done to make sure that people are doing that or following those instructions that you just made up so nicely. It is a toughie. You said it was a toughie when you thought it was the easier one.

DR. LINDENFELD: I know. That is why I answered the easier one. Boy, I don't know. I think whatever we do would have to be done with dofetilide as well, the same issues. I think that what could be done, of course, is to require at least for an initial prescription a QT interval and a calculated creatinine clearance. I think people would be upset by that, but probably -- physicians -- but probably they shouldn't

be because that is what you should have to prescribe it. And if you haven't -- as I said about with the example of the 70-year-old lady, if you haven't sat down and calculated the creatinine clearance, you are going to get a surprise in a lot of these people. So if we are going to do a program, at least -- now it is going to be a problem, because I am not sure that has to be done for every single recurrent prescription. I don't think it does. But at least for an initial prescription, a calculated creatinine clearance and a QT interval for the prescription.

CHAIRMAN PACKER: I am curious, I understand something like this was discussed for dofetilide as well. There is a difference here, and the difference is that this is a drug which is already on the market. And the requirements that you are talking about are not imposed for the present use of the drug although the present use of the drug includes the possibility of doses higher than the ones being recommended for atrial fibrillation, and no such surveillance is mandated at the present time. So we would be in a sort of interesting situation of

requiring greater surveillance for a lower dose in a lower risk patient population, but no surveillance for a higher dose in a higher risk patient population. Now we have done crazy things like that before. I just want to know whether you think we should do a crazy thing like that again.

DR. LINDENFELD: Well, I think maybe we should. I think I understand the point you are making. But also I think as Tom has said several times, this is a population of people -- a population of people with life-threatening ventricular arrhythmias. Indeed, the risk may be higher, but they have a substantial benefit. And here we may have a bigger risk/benefit ratio than in the other population. I think that is possible. So although it is a conundrum, if we were approving this for the first time, I think I would say -- if it were not on the market, I think I would say yes. I mean, we want to do everything we can do. We have said we are not sure this drug has an overall benefit and it does have a risk.

DR. KOWEY: Milton, if you do what you

said in the preceding part, which was to mandate an in-hospital start for all patients, then doing what JoAnn is suggesting isn't really such a big deal. I mean, they are in the hospital and they get a creatinine and they have an EKG. So it is -- this really is a sting, especially for the initial dosing, is if you ever let somebody do it out of hospital. But let me just tell you that having said that you don't want it started out of hospital, unfortunately there will be that that will happen. And I guess the question I have is admitting that, do you want to talk about out-of-hospital starts even though you are not telling people to do that? Because it is going to happen. You see, JoAnn's question is -- JoAnn's answer is easy if you are doing it in the hospital. But what happens if you are starting it out of the hospital, as you are not supposed to be doing. It is sort of an interesting kind of conundrum.

CHAIRMAN PACKER: Right. In other words, the patients who require the greatest -- who would be the source of the greatest concern would be the ones in which the physician isn't doing the right thing in

the first place and therefore is more likely to not -- to continue to do the wrong thing?

DR. KOWEY: Correct. That is correct.

DR. PIÑA: I have a question for Bob.

DR. KOWEY: That is what you have set up basically.

DR. PIÑA: I have a question for Bob. How is the Clozaril program being handled? Is it the pharmacist who has to dispense the drug but can't dispense it unless he or she sees the white count, and in this case it would be the pharmacist who wouldn't dispense the drug until they see the EKG and the creatinine clearance and know the QT and know the creatinine clearance?

DR. FENICHEL: Yes. It is a good question and the answer is I don't know it. I don't know the answer. Clozapine is part of -- I mean, there is something of the sort I described that is in use right now and it is part of Agency folklore, but I personally don't know what the details are.

DR. THADANI: You know, Milton, there are almost 3 million prescriptions written already on the

drug, which is greater than the indicating use of VT. You know, it is mind boggling the numbers. Obviously if you are saying that this drug must be used as an inpatient, then I think we also should say that the patient must have creatinine clearance measured, formula given provided by the company on a little caliper or whatever, and also make sure that the ECG is done before any dose escalation to safeguard the patient, which should not be difficult. Now, if the patient -- if people are going to -- how are you going to collect data on people who are going to use it outside unless the Agency or the company is going to track all the prescriptions outside. It would be impossible. So I think at least inpatient you could try it.

DR. PIÑA: You know, what I do think the company would need to do to my satisfaction -- and even though I do a lot of teaching and sometimes I don't think that physicians always listen to everything that we have to say -- that the company does have to embark on a very strong educational program to teach physicians who are likely to use the

drug how to use it and how to use it appropriately. And I don't care if you have to hand them something to show them how to calculate a creatinine clearance. Even though it is so simple, most people don't know how to calculate a creatinine clearance unless they actually order the 24-hour urine clearance. So other than that, I don't see how you would enforce this.

DR. THADANI: It might work negative against the company. They are already using our prescription and now you are going to decline them.

CHAIRMAN PACKER: Yes. I don't actually think we have to go further with this. I think, Bob, you have a sense of the kinds of discussions that one could have, and I think we have reached the limit as to how precisely we can define it. The last question to the committee, and that is what post-marketing commitments should be made? This would include any of the above-listed in the question or action studies and studies in patient population, head-to-head comparisons. JoAnn, what do you think?

DR. LINDENFELD: Well, I think it would be wonderful to have a study in the actual population of

patients that will be treated average age 75, half or close to half women. That was the one I would like to see most with enough patients at least followed up for a minimum of six months and probably a year.

CHAIRMAN PACKER: We are talking about things that would be required. Would you require that study?

DR. LINDENFELD: I don't think I would require it, no.

CHAIRMAN PACKER: Okay. Who would require -- there are all sorts of studies that one could imagine here and maybe the best thing --

DR. FENICHEL: Well, Milton, we didn't use the word require.

CHAIRMAN PACKER: Soft?

DR. FENICHEL: In part because we have no legal authority to use the word require.

CHAIRMAN PACKER: I understand.

DR. FENICHEL: If it is approved -- and this is important and perhaps I should have mentioned this before you voted about approval, but I don't know that it would have changed the decision or should

have. But the fact is that if you think, well it should be approved but only because we know they are going to do such and such study, well then you shouldn't vote to approve it. We don't have the facility to make conditional approvals. And so all we can do is seek such studies.

CHAIRMAN PACKER: Okay. I think -- let me -- I think the best way, therefore, to do it is to answer the question the way it is framed, which is should certain studies be sought. And let me just propose the following, only because they came up during the course of the meeting. Elderly patients -- should such a study be sought? Anyone disagree? Okay. Interaction studies with calcium channel blockers and/or beta blockers, anyone disagree?

DR. THADANI: I don't know whether we would need with all the calcium channel blockers. I would go for the calcium channel blockers which reduce or affect the AV node. I am not sure the four hydroproteins would make a difference, unless you believe they are both cardio-depressants.

CHAIRMAN PACKER: Okay. Any other

populations that -- yes, please, Michael?

DR. CAIN: I think the other one is the NIH is putting out another application for scores in sudden death in African Americans because of the high incidence or higher incidence of sudden death in blacks, and one of the presumed mechanisms of that is left ventricular hypertrophy, which fits into hypertension, left ventricular hypertrophy, atrial fibrillation, and there really are no or very few data on non-whites. And so I think that becomes critical.

DR. THADANI: One question didn't come up. At least sometimes we use beta blockers and amiodarone in certain populations. There is no data on it. So are we going to say this should not be used concomitantly with amiodarone? Because both could be used for the same indication. And I could see a patient with coronary artery disease goes into a fib and gets put on this drug for whatever reason and later on he might have VT and gets put on amiodarone. Do we need more data? How comfortable do you feel? Or we should make a recommendation that there is no data and should not be used?

CHAIRMAN PACKER: That is really actually more of an addition to the list of calcium channel blockers that there is also no concomitant data on. Any other suggestions or modifications or any other comments? Bob, have we addressed the questions from the Division?

DR. FENICHEL: Yes.

CHAIRMAN PACKER: We are adjourned.

(Whereupon, at 5:28 p.m., the meeting was adjourned.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Cardiovascular and Renal Drugs Advisory Committee Meeting #88

Before: DHHS/PHS/FDA/CDER

Date: April 29, 1999

Place: Bethesda, MD

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