

Question 2: Valdecoxib

JOINT MEETING OF THE ARTHRITIS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

February 16-18, 2005, Hilton Gaithersburg, 620 Perry Parkway, Gaithersburg, Maryland.

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Highlights

- Voting for Question 2A (increased risk of cardiovascular events) was **Yes 32, No 0**.
- Voting for Question 2B (approval for marketing) was for the **First Vote: Yes 15, No 8, Abstain 9**. For the **Second Vote, voting was: Yes 17, No 13, Abstain 2**.
- Around-The-Table 3C Recommendations (risk-management/suitable populations):

Recommendations were carried over from the prior celecoxib recommendations since only incremental recommendations were recorded.

They were allocated to 37 categories (see Attachment 1).

Each category was scored for each member as “Yes”, “No” or “No Comment”.

“No Comment” in many cases might just mean that someone else had made the recommendation earlier and the member felt no need to repeat the recommendation.

There were **175 recommendations (an average of 5/member) for action (“Yes”), and 20 disagreements with prior recommendations by others (“No”)**.

The categories and “Yes vs. No” tabulations were as shown on the following page:

Net Count (Yes - No)	Category
22	1. Black-box warning (25 vs 3)
17	2. Patient Medication Guide (18 vs 1)
16	3. Contraindicated in Cardiovascular Surgery (16 vs 0)
15	4. Ban Direct To Consumer Adverts (19 vs 4)
11	5. Warning for High Dosage (11 vs 0)
7	6. Warning for Long Duration (7 vs 0)
6	7. Warning for High Cardiovascular Risk (6 vs 0)
6	8. Easier-To-Understand Explanation of Risk (6 vs 0)
6	9. Postmarketing studies (6 vs 0)
5	10. Same labeling for NSAIDs (5 vs 0)
5	11. Postmarketing studies (5 vs 0)
4	12. Allow Black-box Removal if Adequate Trials Performed (4 vs 0)
4	13. Second-line Drug (9 vs 5)
4	14. Patient Consent/Attestation (5 vs 1)
2	15. Exclude if at High Cardiovascular Risk (4 vs 2)
2	16. High Dose Contraindicated (3 vs 1)
2	17. Academic Detailing (2 vs 0)
2	18. Educate Healthcare Professionals (2 vs 0)
2	19. Marketing contingent on LT study forthwith (2 vs 0)
2	20. Don't know long-term CV risk (2 vs 0)
1	21. Third-line drug,
1	22. Dear Healthcare Professional Letter,
1	23. OTC Restrictions,
1	24. Define Class,
1	25. Define Mechanism,
1	26. Comprehension Survey,
1	27. Assess/Manage CV Risk,
1	28. FDA Study of Medication Guides,
1	29. Aspirin May Not Reduce CV Risk and May Increase GI Risk,
1	30. Combine COX-2 & Framingham data,
1	31. Do ALLHAT-Type Study,
1	32. Contraindicated in CABG,
1	33. Warn of Risk of Short-acting NSAIDs, &
1	34. Warn of Risk of COX-2 selective traditional NSAIDs.
1	35. Say that Naproxen is Safer than Coxibs (1 vs. 1)
1	36. Long Duration of Therapy Contraindicated (0 vs 2)
	Other (3)

Question 2A: Discussion: Increased risk of CV events with valdecoxib

- **PARECOXIB CONSIDERED WITH VALDECOXIB:** Dr. Shafer asked if they should discuss parecoxib while discussing valdecoxib. Dr. Wood said yes, since

“parecoxib is converted to valdecoxib in the body”.

- **CLEAR SIGNAL ONLY IN CABG SURGERY:** Dr. Shafer said that valdecoxib increases cardiovascular risk in

cardiopulmonary bypass (of which CABG is one type) but “I don’t think the signal is clear otherwise” since “the signal has been weaker than

other studies of approximately the same size” although in “Study 047, there was some increase in C.V. events versus naproxen.”

Question 2A: Voting: Increased risk of CV events with valdecoxib

- All 32 members voted “Yes” without additional comments.

Question 2B: Discussion: Support for marketing of valdecoxib

- **IS CELECOXIB PREFERABLE TO VALDECOXIB?** –

DIFFERENT VIEWS: **Dr. Wood** said that the current data “probably does not” support continued marketing because 1) clear cardiovascular signal in two studies, 2) lack of clear benefit for GI complications, 3) the committee has already “approved” celecoxib that “appears to have a lower signal than the others”. Later he said “it seems highly improbable to me that this drug is safer than celecoxib. It is almost inconceivable to me why somebody would prescribe this drug over celecoxib if you were going to use that”. “....given the size of the signal and somebody used the expression before, the CAB studies may be a canary in a coal mine. It is a high platelet-activated group and that may be just reflecting a model in which it is easier to see a signal than it is in other models”. **Dr. Hennekens** said that while there is no evidence that valdecoxib is safer than celecoxib, “there is also no evidence that it is more harmful”. **Dr. Nissen** agreed as did **Dr. Abramson**. **Dr. Furberg** disagreed and said “we need to face up to the fact that we don’t have good

evidence and take it off the market”. **Dr. Cush** said that since valdecoxib is “equipotent to available drugs” there is “obviously, demonstrated benefit” and he is not convinced of a “significant risk, when the drug is used as indicated”.

- **LITTLE DATA AND NO CLEAR HAZARD IN INDICATED POPULATIONS:**

Dr. Nissen said that valdecoxib was “really tough” because of the absence of data in the indicated populations. The CABG signal was only really strong in the component that included parecoxib.

- **CABG MAY NOT PREDICT SAFETY IN ARTHRITIS: CABG DATA MAY APPLY TO OTHER NSAIDS:**

Dr. Abramson said “it would be not a good precedent, in my view, to remove a drug because there is an alternative without a more serious safety signal”. Because of low-dose aspirin, in the CABG trials patients “had both COX-1 and COX-2 inhibition” and in the CABG setting, the platelets may be “so intensely clotting that the aspirin may have been overridden. But, in effect, these patients were given a COX-mixed inhibition. So since there was no comparator arm in that valdecoxib/parecoxib study, I don’t

know that we can draw a lot of conclusions about the intrinsic safety of this drug in arthritis use over time. I think that was a flawed study to draw specific conclusions about isolated COX-2 inhibition”. Later he suggested that if “high dose Motrin” had been studied in the CABG setting, similar results might have been obtained.

- **VALDECOXIB ALREADY HAS SKIN BLACK-BOX:** Dr. Elashoff pointed out that valdecoxib already has a black-box for skin problems, so that it already has increased risk versus the other drugs.
- **SHOULD MARKETED DRUGS HAVE RENEWAL DATE?** Dr. Farrar said “it is much harder to take a drug off the market without evidence than not to put it on without evidence” and this suggests “that drugs ought to have a renewal date” and he would “strongly recommend consideration of that”.
- **DOUBLE STANDARD FOR CELECOXIB VS. VALDECOXIB?** Dr. Manzi said that the same standard as with celecoxib (keep on market but with black-box and remove black-box when adequate safety data available) should be applied to valdecoxib.
- **CABG RELATIVE RISK 2 FOR VALDECOXIB & 3.7 FOR COMBINATION: CHRONIC DATA LIMITED AND SAFETY DIFFICULT TO ASSESS:** Dr. Fleming responded to Dr. Nissen’s comment that the safety signal was strongest when combined valdecoxib and parecoxib were given, saying that the relative risk in that setting was 3.7 compared with 2 with valdecoxib alone. Both the lack of long-term safety data and the

uncertainty about extrapolating the CABG findings to the arthritis setting is what “we are struggling with”. Dr. Gibovsky expressed concern about Dr. Fleming’s interpretation of the data “in light of what Dr. Packer taught us this morning”. Dr. Fleming said he “just was looking at the evidence in the totality” and “to my way of thinking, that is strong evidence”.

- **ENORMOUS PHYSIOLOGIC DERANGEMENT IN BYPASS:** Dr. Shafer emphasized the “level of physiologic trespass imposed by cardiopulmonary bypass” and the effects “on the entire immune and thrombotic systems”. So he was concerned that if a company studied analgesia in a bypass setting and had a bad outcome, those findings would be applied in other settings – and he had difficulty extrapolating the findings to arthritis.
- **NAPROXEN STUDIES SHOULD BE PART OF NSAID GROUP ANALYSES:** Dr. Shafer also commented “I totally rejected the concept that the naproxen studies should be separated out...”.
- **PROPOSAL TO VOTE ACCOMPANIED BY NEGATIVE SUMMARY:** Dr. Wood then suggested they move to the voting, first noting “remember, the question asked does it support marketing in the U.S., not just is it neutral” and “the question we are being asked here is does the data support marketing the U.S. So it is not just a question-if we have no data at all, that surely wouldn’t support marketing in the United States. So, absence of data is important here, I think, particularly in the presence of

- a safety signal, a strong safety
- **DISCUSSION CONTINUED:** However, several members wanted to continue the discussion. Dr. Hennekens commented that he interprets the valdecoxib data to say “these classes of agents should not be used in cardiac-surgery patients, but they don't bear directly on their utilization in arthritis patients”.
- **SUPPORT WITHDRAWAL VS. SUPPORT MARKETING:** Dr. Ilowite pointed out that the only reason the question says “support marketing” is that FDA wanted to provide the same question for all three coxibs and rofecoxib is not presently marketed; accordingly, the question might easily have said “does it support withdrawal?” “The hurdle is lower if you say, ‘Does it support marketing?’ than if you say, ‘Does it support withdrawal?’”.
- **HURDLE TO WITHDRAW APPROVED DRUG VS. NOT APPROVING UNAPPROVED DRUG:** Dr. Wood asked Dr. Jenkins (FDA) “do you think the hurdle to remove a drug from the market should be higher than the hurdle to get it on the market?” Dr. Jenkins’ comment was unclear. Dr. Wood said “let’s call the question”. Dr. Temple commented that the “standard for approval” is “fairly clear” but that although you can withdraw a drug from the market if the “risk:benefit calculus” changes, these rules are not “quantitative”. In part because of the legal ramifications, he implied that more evidence is required to take a drug off the market.

Question 2B: Voting (in order)(First Vote on 2B): Support for marketing of valdecoxib

- Dr. Abramson: Yes.
- Dr. Nissen: Yes.
- Dr. Elashoff: “I am concerned that we are adding a new risk to something that already has a black-box warning. So I am unclear here.”
- Dr. Gardner: “Pass:
- Dr. Platt: Yes
- Dr. Day: “Abstain”.
- Dr. Furberg: No.
- Dr. Fleming: “Abstain”.
- Dr. Domanski: “Abstain”.
- Dr. Boulware: Yes.
- Dr. Dworkin: Yes.
- Dr. Hoffman: “Abstain”.
- Dr. Manzi: Yes.
- Dr. Farrar: Yes.
- Dr. Holmboe: No “because of the sulfonamide issue and the other black box for cardiovascular”.
- Dr. Gross: No.
- Dr. Wood: No.
- Dr. Gibofsky: Yes.
- Dr. Crawford: No. “ based on the paucity of evidence”.
- Dr. Cush: Yes.
- Dr. Bathon: Yes.
- Ms. Malone: Yes.
- Mr. Levin: No.
- Dr. Ilowite: “Abstain”.
- Dr. D’Agostino: “Abstain”.
- Dr. Morris: Yes.
- Dr. Cannon: Yes.
- Dr. Shapiro: No.
- Dr. Paganini: “Abstain”.

- Dr. Friedman: “Abstain”.
- Dr. Hennekens: Yes.
- Dr. Shafer: Yes.

Question 2C: General Discussion: Risk-management and suitable populations for valdecoxib

- **REQUEST TO JUST ADD VALDECOXIB RESTRICTIONS:**
Dr. Wood suggested that they “go around the table again and ask for suggestions as to how you would manage this”. “I will assume that we would do at least what we would do with celecoxib unless someone sees an objection to that. Let’s only produce incremental changes, if any, that you would like to see to this”.
- **STUDIES-TO-DO DISCUSSION:**
Dr. Temple suggested that the

committee might care to consider here “what studies people should do” even though this will be discussed later in Question 5. Dr. Wood declined this suggestion “because I want to keep us moving”. He asked members to add “to your previous comments .. if there are things you want to add, add them. Otherwise, we will just stay with what you said before”.

Question 2C: Around-the-table comments by committee (only comments additional to those for celecoxib included): Risk-management and suitable populations for valdecoxib

DR. SHAFER: “in anesthesia, we do desperately need better options in the immediate post-operative period for which the intravenous form is an intriguing opportunity”.

DR. HENNEKENS: Same as for celecoxib.

DR. FRIEDMAN: Same as for celecoxib.

DR. PAGANINI: “alter the black box to include only post-cardiac surgery”.

DR. SHAPIRO: “exclude its use ever in post-cardiac surgery”.

DR. CANNON: Same as for celecoxib.

DR. MORRIS: “I would suggest a medication guide. I would also suggest a contraindication that would be both in the contraindications section and the black box in cardiac surgery. I would also try to develop some kind of special program that would be coordinated with patients undergoing cardiac surgery that would have some kind of extra warning.”

DR. D'AGOSTINO: Same as for celecoxib.

DR. ILOWITE: “discussion of the CABG data”.

MR. LEVIN: Same as for celecoxib.

MS. MALONE: “emphasize the need for postmarketing surveillance”.

DR. BATHON: “black-box warning for this drug with the advisory about the CABG patients and against chronic use until further safety data are available in the target populations”.

DR. CUSH: “change the warning to a black box regarding CABG and any other acute cardiac situation”.

DR. CRAWFORD: Same as for celecoxib.

DR. GIBOFSKY: Same as for celecoxib.

DR. WOOD: “triple black-box warning”.

DR. GROSS: “make valdecoxib a second-line selective COX-2 inhibitor”.

DR. HOLMBOE: “contraindicate this drug for use in post-CABG surgery”. Ban for “consumer advertising”. “I clearly would make this a second-line drug”.

DR. FARRAR: In the black box: “an absolute contraindication in cardiac surgery”, “a contraindication stating that the long-term-use risk is unknown” and “second-line”. Clear indication that, “if the company produces data obviating those, then those could be removed.”

DR. MANZI: “contraindication in any revascularization procedure”.

DR. HOFFMAN: “whereas I was not in favor of a duration limitation for Celebrex, I am in favor of a duration

limitation for this agent for which we only have six-month data”.

DR. DWORKIN: “black-box warning”, “third-line” and “with the contraindications that other people have mentioned”.

DR. BOULWARE: “contraindication for CABG surgery” and “listing that we don't know the long-term use in cardiovascular risk”.

DR. DOMANSKI: “Number one, I am going to ask that I be allowed--I am given pangs of conscience by Dr. Nissen. I think he is right. I don't think the data are there and I would like to change my abstain to a no, if I am permitted to. With regard to the box, same as Celebrex but would add that it is contraindicated in the setting of post-bypass.”

DR. FLEMING: “contraindicated in cardiac surgery”, “mandated requirement ... for trials that would give us the broader insight that we are lacking. I am troubled by the fact that when we look at the other four coxibs, they have all had, on average, 20,000 patients. We have three here. Dr. Nissen has persuaded me that we do need to be more forthcoming. We can't probably be as persuasive in mandating that as we can in voting no. So, with that logic, I would like to also change my ‘Abstain’ to a ‘No’.”

DR. FURBERG: “limitation in use to 1 to 2 weeks”, “mentioning in the black box or somewhere in the labeling that there is a lack of evidence for short- and long-term benefit and safety in low-risk patients”.

DR. DAY: “contraindications that others have mentioned”, “no DTC”.

DR. PLATT: “contraindication for patients undergoing cardiovascular surgery”, make “continued marketing of this drug conditional on an appropriately designed randomized trial being undertaken forthwith”.

DR. GARDNER: “I will join my colleagues in converting from an ‘Abstain’ to a ‘No’ and, therefore, not make recommendations for continued”.

DR. WOOD: That was another change in the vote. Did you get that? You can

see how hanging chads come; right? Dr. Gardner changed her vote from an ‘Abstain’ to a ‘No’.

DR. ELASHOFF: “limitation to second-line therapy”.

DR. NISSEN: “stronger warning than we put on celecoxib which particularly emphasizes that longer-term safety has not been established and that the drug should not be used long-term until further data are forthcoming”.

DR. ABRAMSON: Same as for celecoxib.

Question 2B: Valdecoxib: Clarification of Dr. Elashoff’s vote

Dr. Wood announced that “Dr. Elashoff’s vote was not properly recorded because it was unclear what she said, apparently. Would she like to vote?”. Dr. Elashoff said “I was told I

had to say something other than “unclear,” so I said no.” Dr. Wood then said “the vote is 14 yes, 5 abstain and 12 no”.

Question from Dr. Hennekens about Class Effect in CABG Patients

Dr. Hennekens wanted to make sure that people would know that they should not substitute “another coxib or another NSAID instead of valdecoxib “. Dr.

Wood and Dr. Jenkins seemed to agree that FDA would “contraindicate all of them in cardiac surgery”.

Question 2B: Valdecoxib Revote

The initial vote on the marketing of valdecoxib was disregarded, and voting was performed a second time. All 32 valdecoxib votes had been recorded before a decision was made to vote again. 31 votes were clearly stated at the initial vote. A few minutes later, Dr. Wood (the Chairman) announced that

“Dr. Elashoff’s vote was not properly recorded because it was unclear what she said, apparently”. When she was asked to make a clear vote in response to this problem, she voted “No”.

Following this, the first valdecoxib 2B vote, as given to and announced by Dr.

Wood was: “14 Yes, 5 Abstain, and 12 No” which did not provide a majority in favor of marketing valdecoxib. Note that, based on both the audio record and the official transcript, this tally is incorrect – the actual vote was 15 Yes, 10 Abstain, and 7 No.

The Committee then went on to discuss labeling restrictions for valdecoxib (Question 2C) and then Vioxx (Questions 3A and 3B). During these discussions, and prior to the 3B vote and repeat 2B vote, the following interaction between Dr. Wood and Dr. Nissen took place:

Dr. Nissen: You know, I’m disappointed in the abstentions. You know, we’ve all sat here and listened to the evidence, you know, we have. ...

Dr. Wood: Steve, I don’t think we should, should badger people into voting...

Dr. Nissen: Well, I actually I do want to ask people as we move forward to think about making a commitment one way or the other. Because, what you have is a minority of us making a decision. And I think it is appropriate that people weigh in. So, one man’s opinion....

After voting on Questions 3A and 3B, the following discussion took place:

Dr. Wood: The hanging chads are... have raised their head. They want to go back. We can’t agree on the vote apparently for 2B. That was... So, the Question for 2B was, em, "Does the

overall risk versus benefit profile for valdecoxib support marketing in the US". Even though we announced the vote and everybody rushed out to file a story, em, <Dr. Wood laughs> it was premature. We’re going to have to retake the vote because we’re not sure what the vote was, apparently. So, so, em, I’ve forgotten which side we started on now. Who started? All right, Steve. So, <a Committee member laughs> let’s go round again, and you’ll vote. And let me remind everybody what we’re voting here. We’re voting for valdecoxib: Does the overall risk versus benefit profile for valdecoxib...

Questions to Dr. Wood: (inaudible).

Dr. Wood: Yes. We’re.. Vald... We’re going back to retake the vote for valdecoxib for question 2B, em, because there’s some discrepancy apparently in the vote counting. Remember Florida? You thought I was kidding, right?

Questions to Dr. Wood: (inaudible).

Dr. Nissen: Where, where’s Katherine Harris now that we need, need her?

Dr. Wood: Right. So we’re going to go back to retake. Isn’t that right? (obviously asking for confirmation from some person he was looking at). We’re going back to 2B. We’re going back to

the question 2B. And we're taking the, the vote on 2B. So the question is: For valdecoxib, Bextra, does the overall risk versus benefit profile for valdecoxib support marketing in the US? A Yes would keep it on the market. A No would take it off the market. And Steve, were you the... which one was it?

Question from a Committee Member: Is it not on the tape recorder?

Abramson: Abramson, Yes.

<Voting proceeds to completion. The Committee votes in favor of valdecoxib marketing.>

<Further discussion and voting on Vioxx>

Dr. Wood: OK. And I'm now in a position to read you the votes for the, for t.. Question 2B and 3B, at least for now. Em, the, the, em vote for 2B, which was the vote on valdecoxib (for those of you who've forgotten already) em was 17 Yes, 2 Abstain and 13 No....

The actual revote regarding support for valdecoxib marketing proceeded as follows:

DR. ABRAMSON: Yes.

DR. NISSEN: Yes.

DR. ELASHOFF: No.

DR. GARDNER: No.

DR. PLATT: Yes.

DR. DAY: Abstain. "the hanging chad. I have to abstain because the question is based on the available evidence. That is the basis for my abstention."

DR. FURBERG: No.

DR. FLEMING: No.

DR. DOMANSKI: No.

DR. BOULWARE: Yes.

DR. DWORKIN: Yes.

DR. HOFFMAN: Yes. "with restrictions on dose and duration".

DR. MANZI: Yes.

DR. FARRAR: Yes. "with limitations on dose and duration".

DR. HOLMBOE: No.

DR. GROSS: No.

DR. WOOD: No.

DR. GIBOFSKY: Yes.

DR. CRAWFORD: No.

DR. CUSH: Yes.

DR. BATHON: Yes. "I had restrictions, also".

MS. MALONE: Yes.

MR. LEVIN: No.

DR. ILOWITE: Yes “I am one of the abstainers before. I will change it to yes”.

DR. D'AGOSTINO: No. “I will balance that and change it to no”.

DR. MORRIS: Yes.

DR. CANNON: Yes.

DR. SHAPIRO: No.

DR. PAGANINI: Abstain. “Paganini continues abstaining”.

DR. FRIEDMAN: No. “I will go to a no”.

DR. HENNEKENS: Yes.

DR. SHAFER: Yes.

Discussion Text: Question No. 2: Valdecoxib

Question 2A Discussion

DR. WOOD: Question No. 2 addresses valdecoxib. The first question is, do the available data support a conclusion that valdecoxib significantly increases the risk of cardiovascular events. I think we have probably had a lot of the discussion on this so let's see if there is any new discussion that we would like to have and then we can, perhaps, go around the table and get everybody's brief individual comments on this. Is there discussion first? Then let's go around the table--I beg your pardon. Yes?

DR. SHAFER: One point of discussion. Can we also discuss parecoxib, or think about parecoxib concurrently. I know it is not an approved drug but at least some of my thinking about this relates to my thoughts about parecoxib as well. Or is that not appropriate?

DR. WOOD: Sure. I mean parecoxib is converted to valdecoxib in the body. Do you think there is a difference?

DR. SHAFER: That answers my question.

DR. WOOD: Pardon?

DR. SHAFER: That answers my question when it comes time for the vote. Question 2A Voting

DR. WOOD: Okay. Go ahead. We will start with you this time, Steve.

DR. SHAFER: All right. The question before us is do the available data support a conclusion that it significantly increases the risk of cardiovascular events. Yes, after cardiopulmonary bypass. I point out that CABG is just one type of cardiopulmonary bypass but it is probably common to all forms of cardiopulmonary bypass because the common thread is the bypass machine, itself. I don't think the cardiovascular signal is clear otherwise so I would say yes in the setting of cardiopulmonary bypass.

DR. WOOD: Let me just ask you. Why did you not see a signal anywhere else

given that there wasn't any evidence anywhere else.

DR. SHAFER: That is what you just said. There was no signal anywhere else because there was no evidence anywhere else.

DR. WOOD: So it is not that you think that it is safe in other settings. It is just that you don't know.

Question 2A Voting

DR. WOOD: Charlie?

DR. HENNEKENS: Hennekens. Yes.

DR. FRIEDMAN: Friedman. Yes.

DR. PAGANINI: Paganini. Yes.

MS. SHAPIRO: Shapiro. Yes.

DR. CANNON: Cannon. Yes.

DR. MORRIS: Morris. Yes.

DR. D'AGOSTINO: D'Agostino. Yes.

DR. ILOWITE: Ilowite. Yes.

MR. LEVIN: Levin. Yes.

MS. MALONE: Malone. Yes.

DR. BATHON: Joan Bathon. Yes.

DR. CUSH: Cush. Yes.

DR. CRAWFORD: Crawford. No relation to Lester. Yes.

DR. SHAFER: The other places where they have looked at it, the signal has been weaker than other studies of approximately the same size as I interpreted the data, although Study 047, there was some increase in C.V. events versus naproxen.

DR. GIBOFSKY: Gibofsky. Yes.

DR. WOOD: Wood. Yes.

DR. GROSS: Gross. Yes.

DR. HOLMBOE: Holmboe. Yes.

DR. FARRAR: John Farrar. Yes.

DR. MANZI: Sue Manzi. Yes.

DR. HOFFMAN: Gary Hoffman. Yes.

DR. DWORKIN: Dworkin. Yes.

DR. BOULWARE: Boulware. Yes.

DR. DOMANSKI: Domanski. Yes.

DR. FLEMING: Fleming. Yes.

DR. FURBERG: Furberg. Yes.

DR. DAY: Day. Yes.

DR. PLATT: Platt. Yes.

DR. GARDNER: Gardner. Yes.

DR. ELASHOFF: Elashoff. Yes.

DR. NISSEN: Nissen. Yes.

DR. ABRAMSON: Abramson. Yes.

Question 2B Discussion

DR. WOOD: The second question is, does the overall risk versus benefit profile for valdecoxib support 288 marketing in the U.S.? I think we should do some discussion on that first. Comments on that? I guess I would comment. I am not sure that the current data we have does support continued marketing in the U.S. In fact, I think it probably does not. We have got a very clear and replicated signal of cardiovascular lack of safety in two studies and we have got a lack of clear G.I. benefit in terms of complicated risks. And we have already approved one drug which appears to have a lower signal than the others. It would seem to me that, if this drug were to be continued to be marketed, we would need a lot better data to justify its continued availability Dr. Nissen?

DR. NISSEN: This one is really tough because there is just not any data in the population to which this drug is being used. The only data we have is two studies, one of which was small, the other of which was, I think, pretty clear after cardiopulmonary bypass and that signal was very strong really only in the arm that got the I.V. product. So what really have is an absence of information. Now, the question I think you are asking, Alastair, is was there a mistake made in actually approving this drug with the limited data that was available because that is really what you are saying, that in the absence of proof that it is safe, that it should be deregistered. I think that is really tough. So I have a lot

of trouble with this one because I don't see evidence one way or the other for valdecoxib. Now, maybe somebody can help me. Tom, you can do some mathematical high jinks over there and maybe you can convince me to the contrary, or Ralph or Charlie, but I don't have evidence.

DR. WOOD: Just to respond to that, I think we have heard the argument many times that people need choices. I agree with that. But it seems highly improbable to me that this drug is safer than celecoxib. It is almost inconceivable to me why somebody would prescribe this drug over celecoxib if you were going to use that. I am not arguing whether you should use celecoxib or not. We have been through that discussion. But, given the size of the signal and somebody used the expression before, the CAB studies may be a canary in a coal mine. It is a high platelet-activated group and that may be just reflecting a model in which it is easier to see a signal than it is in other models and it was possible, remember, to see it with a relatively small number of patients, 500 patients, or something. So this was a very strong signal in a very small number of patients, a fifth of the number of patients seen in the approved study, for example.

DR. HENNEKENS: Alastair, you are quite right that there is no evidence that it is safer than celecoxib, but there is also no evidence that it is more harmful than celecoxib.

DR. NISSEN: Exactly.

DR. WOOD: Dr. Abramson.

DR. ABRAMSON: I would agree. I think there is a strong database in terms of the clinical trials. What we are lacking are large outcome trials that show a VIGOR-like or a TARGET-like effect. So, therefore, it would be not a good precedent, in my view, to remove a drug because there is an alternative without a more serious safety signal. I think there is a caveat with these CABG trials that we have to talk about which is that these patients, as we stressed yesterday, or the other day, were given low-dose aspirin. So, in effect, they had both COX-1 and COX-2 inhibition. It may be that, in that acute event, the platelets are so intensely clotting that the aspirin may have been overridden. But, in effect, these patients were given a COX-mixed inhibition. So since there was no comparator arm in that valdecoxib/parecoxib study, I don't know that we can draw a lot of conclusions about the intrinsic safety of this drug in arthritis use over time. I think that was a flawed study to draw specific conclusions about isolated COX-2 inhibition.

DR. WOOD: But the company had so little faith in the safety of the drug that they gave it with aspirin in the general surgery study.

DR. ABRAMSON: Nevertheless, it was a mixed compound.

DR. WOOD: They didn't feel it was safe to give to patients who were undergoing general surgery without aspirin.

DR. ABRAMSON: Right. But if we are doing clinical pharmacology and using that to make projections on safety of drugs, those patients were given mixed inhibitor.

DR. WOOD: Sure. Dr. Furberg?

DR. FURBERG: I agree with Dr. Nissen that we have an absence of good evidence but I come down on the other side, and that is not a reason for leaving it on the market, a lack of evidence. So I think we need to face up to the fact that we don't have good evidence and take it off the market and the manufacturer can come back when they have good data.

DR. WOOD: Yes; motivate them. Dr. Elashoff?

DR. ELASHOFF: Doesn't this drug already have a black-box warning that the others do not?

DR. WOOD: No; a black-box warning for skin, not for cardiovascular.

DR. ELASHOFF: Yes, but I mean isn't that something that should be taken into account in terms of the risk:benefit for this particular drug.

DR. WOOD: Right. So there are additional risks, you are saying. Yes; that's right. Any other comments? Dr. Farrar?

DR. FARRAR: I think that this drug, in particular, also points out another suggestion that should be made and would make me feel a lot better. I think it is much harder to take a drug off the market without evidence than not to put it on without evidence. That makes it a quandary for me but it also suggests, in

fact, that drugs ought to have a renewal date. Our grants have a renewal date, lord knows. and we have to show that we have made progress. I would actually strongly recommend consideration of that. Obviously, that discussion is later but it would make me feel a lot better about this.

DR. WOOD: Dr. Cush?

DR. CUSH: This question speaks to risk:benefit and there is, obviously, demonstrated benefit as these drugs are, again, equipotent to available drugs. I am not convinced that there is a signal that says that there is a potential risk, a significant risk, when the drug is used as indicated.

DR. WOOD: Any other comments? Then let's go around the room--oh; sorry. Dr. Fleming? Let Tom go first and then Dr. Manzi next.

DR. FLEMING: Go ahead.

DR. WOOD: Dr. Manzi, you have been deferred to.

DR. MANZI: I just wanted to respond to the comment that we need to wait until they can prove safety. I would say that we put the same charge to Celebrex in removal of the black-box warning, that we saw a signal, we felt that there was clearly a risk and now we want long-term safety data. I think we should do the same with this drug.

DR. WOOD: Dr. Fleming?

DR. FLEMING: I appreciate the fact that we have much more limited data here, I think about 3,000 patients. It is predominantly in the CABG setting. The

signal, though, here, really impresses me with the magnitude of the signal. We are looking at the 035 trial at a 15 to 2 on events and that is 1-1 on M.I. It doesn't reflect the fact that the investigators called 9 to 2 on those MIs. When we are looking at the other data as well, we have got quite a strong signal. The 069 trial was in general surgery and that was more neutral at 5-5, although DVTs were 2 to 1 for placebo. I know these are really small numbers but when you are looking at the events that are of greater interest, the MIs, the arrests, the cardiac deaths and the strokes, it is 3 to 2 so, again, it is really small data. But I don't consider that favorable. It is in the wrong direction. Essentially, we have the 035 trial and the Nussmeier trial. Steve Nissen pointed out that it is relevant to look at the fact that we had the three arms. The combination arm had a relative risk of 3.7. The valdecoxib had a relative risk of 2. So it was less striking although, when you looked at all of the events, it was a relative risk of 1.9 in both. So, essentially, there is very strong evidence here in the setting where it has been studied. What we are struggling with is that there is very limited evidence, though, in being able to look beyond. So what do you say? I mean essentially where there is evidence, it is of significant concern, but this is understudied relative to other agents. And so do we give it the benefit of the doubt, or do we view that in the absence of reliable evidence here? Continued marketing is of serious concerns, and we should wait until we have more reliable evidence to restore marketing. To me that's the debate.

DR. WOOD: And the drug clearly gives bigger signals than you see anywhere else. The general surgery study was so

underpowered you couldn't possibly have seen anything, given the agent and so on.

DR. FLEMING: And I guess my point there is it's not a reassuringly positive study.

DR. WOOD: Right, not reassuring, and they were on aspirin.

DR. FLEMING: The key events are 3 to 2 in the wrong direction, and it's in the context of aspirin.

DR. WOOD: Right. I mean, you know, come on. Okay.

DR. : You know, I think that given the extensiveness of the review that we've had, I think it's reasonable not to accept the precedent that it's already on the market and to make an independent recommendation about whether it should be regardless of what that turns out to be. But I think we--you know, given again the extent of this review, it's appropriate to give it that kind of de novo review and decide whether it should be there.

DR. WOOD: Okay. Dr. Gibofsky?

DR. GIBOFSKY: I have a question for Dr. Fleming. Is it possible?

DR. : Sorry. Yes, go ahead.

DR. GIBOFSKY: Dr. Fleming, in light of what Dr. Packer taught us this morning, if you apply, again, having only one time point to look at, and you're applying a second level of discrimination at a .05 level, do we have enough of a power--or a signal here that it does become significant? I mean I'm

impressed by some of the participants say that this is a much bigger signal we are seeing in other situations, which admittedly is lower at 1.4, as many of you said, but I'm not impressed that it's such a large signal, one-time signal, that it merits the drug being dropped from the market.

DR. FLEMING: Let me respond to that in one minute.

DR. WOOD: Okay, all right. And other questions? Yes, Dr. (?).

DR. : Yes. I share Dr. Abramson's and Nissen's concerns. I also am mindful of the volumes of data that we have reviewed. However, at the end of the day, as we've heard from one speaker in particular, we're obliged to make our decisions based on the weight of the evidence, and we practice evidence-based medicine. We don't practice the absence of evidence-based medicine. So consequently I think we have to look at the data that we have, be cautious, be concerned, have that discomfort in our gut, but go with the evidence and the data that we have.

DR. WOOD: I agree with that and we have no evidence of G.I. safety. We have evidence of cardiovascular toxicity and that, to me, is compelling. Dr. Shafer?

DR. SHAFER: I just want to respond to the canary in the coal mine and the cardiovascular safety concerns because it really was the two CABG studies. The level of physiologic trespass imposed by cardiopulmonary bypass should not be underestimated or the effects of that on the entire immune and thrombotic systems. So, if the message to a company is don't ever study a drug in

cardiopulmonary bypass patients because, if you get a bad outcome, it will be assumed to be a representative of your class of drugs and there will be no more studies of analgesic possibilities in patients on cardiopulmonary bypass. So I totally rejected the concept that the naproxen studies should be separated out as a different sort of funny class effect. But in the case of cardiopulmonary bypass, I really do think that is a very different kettle of fish. I don't think it is a canary in a coal mine although I could be proven wrong by future data. But do not underestimate the level of trespass that that represents and the limits that that puts on the extrapolatability of those data to patients on arthritis, or with arthritis.

DR. WOOD: Any other comments? Dr. Abramson?

DR. ABRAMSON: The point I was making about the aspirin is that I am not sure that we can use this CABG study as a surrogate for the safety of these drugs in the long term because there was no nonselective comparator. Had we done the same study with Motrin at high doses, because the COX-2 effect seems to be driving it and aspirin did not prevent the adverse event, I am concerned that, alone, without a comparator, it doesn't help us say what this drug does in the non-acute coronary-syndrome setting because this was a dual-inhibiting setting. So I think we have to be cautious in extrapolating that as a surrogate study.

DR. WOOD: Although it is interesting that the general-surgery patients also got aspirin.

DR. ABRAMSON: But they did not have the same strength of signal.

DR. WOOD: Oh, no; but that there was a need to give them aspirin.

DR. ABRAMSON: We don't know, Alastair, if there was a need to give it or not. They gave it. That is all we can say. We don't know what would happen without aspirin. Steve, your points are well-taken. I am very troubled by this one because, as a cardiologist, I know what happens when you open a chest and stop the heart and put people on bypass pumps and blood circulating extracorporeally. It is a really very big insult. So it is very hard for me to extrapolate results in that population to a general population. I agree with everything that has been said. It is a very strong signal and I was the one that said, the other day, that this happened with 10 days of exposure in the face of aspirin. That is a very compelling result. But I don't know how to apply that knowledge to patients that are going to get 10 or 20 milligrams of the drug with arthritis. What I do know is that giving 40 milligrams right after cardiopulmonary bypass is not a good idea. I know that for certain. But I don't know what that needs for taking 10 or 21 milligrams with arthritis. So what it really comes down to is how much weight do you all give to this notion of the class effect? If you really, really believe that there is unequivocal evidence of a class effect, then if see it in any population for any drug in the class, then, you got to do that. But I must point out to you that we don't have long-term safety data on ibuprofen or diclofenac. Does that mean we should deregister those drugs? I think it is a really interesting issue.

DR. WOOD: Let's go to the question, then. The question is, does the overall risk:benefit profile for valdecoxib support--remember, the question asked does it support marketing in the U.S., not just is it neutral. Let's start with Dr. Abramson.

DR. CUSH: Wait. Dr. Fleming was going to give us an answer, maybe.

DR. WOOD: Oh, I'm sorry. You're right. Sorry, Tom.

DR. FLEMING: I just was looking at the evidence in the totality. Essentially, the totality of the evidence, the problem is it is very limited. We have got, in what has been presented to us, three trials; the Nussmeier 071 trial, 035 trial, the 069. By my crude summary here, the relative risk is slightly more than 2.5 and, in terms of strength of evidence, the standard error is more than 3.0. So, to my way of thinking, that is quite strong evidence. I would surely like to have a lot more data and my biggest uncertainty is how does this extrapolate to other settings. But there is quite strong data here in the CABG setting, in the surgery setting.

DR. SHAFER: How much of that is driven by the CABG study?

DR. FLEMING: Well, there are two and almost all the data are from those two. The general-surgery study, I counted as 5.5 although, really, the events we are interested in are 3 to 2. So this is a slightly--it is.

DR. WOOD: But the question we are being asked here is does the data support marketing the U.S. So it is not just a question--if we have no data at all, that

surely wouldn't support marketing in the United States. So, absence of data is important here, I think, particularly in the presence of a safety signal, a strong safety signal.

DR. CUSH: Absence of data means you take a drug off the market?

DR. WOOD: That is what we will have to decide. Dr. Gibofsky.

DR. GIBOFSKY: I have made my comments..

DR. WOOD: Sorry. Dr. Hennekens?

DR. HENNEKENS: I believe there is a class effect which is similar for all the coxibs and the short-acting NSAIDs. As such, I interpret the valdecoxib signal to be that these classes of agents should not be used in cardiac-surgery patients, but they don't bear directly on their utilization in arthritis patients, in my view.

DR. WOOD: Dr. Ilowite?

DR. ILOWITE: Dr. Wood, you are, I think, getting back to Dr. Temple's wording of the questions. The only reason it says "support marketing" is because he didn't want to change the format of the questions for the three drugs. So it might have easily said, "does it support withdrawal?" The reason that wasn't done was because--

DR. WOOD: But it doesn't. I mean, he didn't want to change--well, that is fine. I think people know what we are voting on so I don't think it makes much difference. Do we want to have a discussion on this point? Go ahead, Dr. Ilowite, again.

DR. ILOWITE: One is more of a passive effect. The hurdle is lower if you say, "Does it support marketing?" than if you say, "Does it support withdrawal?"

DR. WOOD: That's right. But if we think that is truly different, then what we are saying is that the hurdle to remove a drug that we see as being unsafe, we are going to make that hurdle substantially higher than the hurdle to get it on the market in the first place. That is an interesting concept and one that we should, perhaps, discuss, but I am not sure that is--do you think, Bob--Bob Temple--do you think--Dr. Jenkins, do you think the hurdle to remove a drug from the market should be higher than the hurdle to get it on the market?

DR. JENKINS: That is a very interesting and difficult question because, obviously, the product is already on the market. You are fundamentally being asked, given that you voted in 2.a. that you think that the drug increases the risk of cardiovascular events, should that have any impact on whether it remains on the market.

DR. WOOD: Is your proposal, Dr. Ilowite, that we change the question to should--or do you just want us--

DR. ILOWITE: No; the question was fine.

DR. WOOD: Then let's call the question.

DR. TEMPLE: Alastair, just one thing.

DR. WOOD: Yes, Bob.

DR. TEMPLE: In legal terms, as opposed to practical terms, it is fairly clear that the standard for approval says, all tests reasonably applicable have been done to evaluate safety and it is safe, and it has got to be effective. It is very clear from the law and court decisions that one of the things you could do, if you got more information that make you doubt that the risk:benefit calculus you made at the time of approval was still true, you could seek to withdraw it from the market. These rules and the law doesn't give quantitative differences there. Of course, to take something off the market against the company's will, you have to go through a legal set of proceedings. Therefore, you queried about the evidence arguably more than you are when you first do the approval decision. So there is a fair amount of evidence that you need to take a drug off the market as a practical matter. Now, you know, in a different world where, at five years, you reconsider it just as though you didn't know anything, starting from the beginning, maybe the standards would be different.

DR. WOOD: But, from a patient's perspective, it is probably the same thing.

DR. TEMPLE: You, certainly, intellectually want to think of it as roughly the same thing. There is, of course, the fact that after a drug is marketed, you have certain assurances from spontaneous reports that you didn't have before you marketed that is irrelevant to these considerations, I would say.

Question 2B Voting (First Time)

DR. WOOD: Okay. Let's start the vote from Dr. Abramson. So the question is, still as written, does the overall risk support marketing in the U.S. A yes would mean leaving it on the market. A no would mean taking it off the market, just to make sure.

DR. ABRAMSON: Yes.

DR. NISSEN: Yes.

DR. ELASHOFF: I am concerned that we are adding a new risk to something that already has a black-box warning. So I am unclear here.

DR. GARDNER: Pass.

DR. PLATT: Yes.

DR. DAY: Abstain.

DR. FURBERG: Furberg. No.

DR. FLEMING: Fleming. Abstain.

DR. DOMANSKI: Domanski. Abstain.

DR. BOULWARE: Boulware. Yes.

DR. DWORKIN: Dworkin. Yes.

DR. HOFFMAN: Abstain.

DR. MANZI: Manzi. Yes.

DR. FARRAR: Farrar. Yes.

DR. HOLMBOE: Holmboe. No, because of the sulfonamide issue and the other black box for cardiovascular.

DR. GROSS: Gross. No.

DR. WOOD: Wood. No.

DR. GIBOFSKY: Gibofsky. Yes.

DR. CRAWFORD: Crawford. No, based on the paucity of evidence.

DR. CUSH: Cush. Yes.

DR. BATHON: Bathon. Yes.

MS. MALONE: Malone. Yes.

MR. LEVIN: Levin. No.

DR. ILOWITE: Ilowite. Abstain

DR. D'AGOSTINO: D'Agostino. Abstain.

DR. MORRIS: Morris. Yes.

DR. CANNON: Cannon. Yes.

DR. SHAPIRO: Shapiro. No.

DR. PAGANINI: Paganini. Abstain.

DR. FRIEDMAN: Friedman. Abstain.

DR. HENNEKENS: Hennekens. Yes.

DR. SHAFER: Shafer. Yes.

Question 2C Discussion - General

DR. WOOD: If yes, and all those who abstained and voted no can participate in this as well, describe the patient population in which the potential benefits of valdecoxib outweigh the potential risks and what actions you recommend that FDA should consider implementing to ensure safe use of valdecoxib? Let's see if there is discussion on this or whether we want to do the same as we did with the last one and go around again and each person give their recommendations as to what restrictions, if any, they would like to see on the prescribing. Is that acceptable to the committee?

DR. HENNEKENS: Could I ask a question about procedure, Alastair?

DR. WOOD: Assuming that there is no objection to that, let's go around the table again and ask for suggestions as to how you would manage this. I guess what I would do here is, I am going to-- if people are agreeable, I will assume that we would do at least what we would do with celecoxib unless someone sees an objection to that. Let's only produce incremental changes, if any, that you would like to see to this. Bob?

DR. TEMPLE: You are going to discuss this in a later question, No. 5, like what studies should people do. I just wonder whether you want to speculate on that a little bit so that people can think about that as they give this answer. For example, do you mean a comparison with naproxen? Or what?

DR. WOOD: Of course. Go ahead.

DR. HENNEKENS: If a person feels that they don't have enough information to really make a judgment about whether the drug should be on the market or not and, therefore, abstain, are they necessarily in a position that they could then say which patient populations would benefit from it?

DR. WOOD: Yes; I think they are. I think they can provide us with guidance to what should be done if the drug were to stay on the market. They could still provide us with guidance, yes. So I think we should be encompassing. Everybody has the chance to respond.

DR. WOOD: The committee, you mean, or me?

DR. TEMPLE: Huh?

DR. WOOD: The committee or me?

DR. TEMPLE: Everybody. I am only asking now, even though it is there later, because maybe that is relevant to the discussion that goes on as it might have been the celecoxib discussion, too.

DR. WOOD: Okay. Boy, that might make it complicated, I mean, because we--

DR. TEMPLE: You can duck it if you really want to.

Question 2C: Around The Table Suggestions by Committee Members

DR. WOOD: Let's go around and make the recommendations here and then--we are not going to forget that--because I want to keep us moving. Otherwise, we will never get to these other things. Let's start with Steve Shafer and go around. Steve, to save time, set the tone by adding to your previous comments rather than--if there are things you want to add, add them. Otherwise, we will just stay with what you said before.

DR. SHAFER: My comments are the same as my previous comments with the one addition that, in anesthesia, we do desperately need better options in the immediate post-operative period for which the intravenous form is an intriguing opportunity. I will just say that.

DR. HENNEKENS: Hennekens. I make the same recommendations as for celecoxib.

DR. FRIEDMAN: Friedman. Same recommendations.

DR. PAGANINI: Paganini. I would alter the black box to include only post-cardiac surgery. I don't see that there is any other data on there for anything else.

DR. WOOD: Dr. Shapiro? MS. SHAPIRO: I would mimic what I had said before and exclude its use ever in post-cardiac surgery.

DR. WOOD: Dr. Cannon?

DR. CANNON: Same as my comments for celecoxib.

DR. WOOD: Dr. Morris?

DR. MORRIS: I would make some changes. For this one, I would suggest a medication guide. I would also suggest a contraindication that would be both in the contraindications section and the black box in cardiac surgery. I would also try to develop some kind of special program that would be coordinated with patients undergoing cardiac surgery that would have some kind of extra warning.

DR. WOOD: Dr. D'Agostino.

DR. D'AGOSTINO: D'Agostino. Nothing to add.

DR. ILOWITE: Ilowite. Nothing to add except discussion of the CABG data.

DR. WOOD: Arthur?

MR. LEVIN: Levin. Nothing to add.

DR. WOOD: Ms. Malone.

MS. MALONE: Malone. Much the same as with Celebrex but to also emphasize the need for postmarketing surveillance.

DR. WOOD: Dr. Bathon.

DR. BATHON: I would be in favor of a black-box warning for this drug with the advisory about the CABG patients and against chronic use until further safety data are available in the target populations.

DR. WOOD: Dr. Cush.

DR. CUSH: The same but I would then change the warning to a black box regarding CABG and any other acute cardiac situation.

DR. WOOD: Dr. Crawford.

DR. CRAWFORD: Same as my comments with celecoxib.

DR. WOOD: Dr. Gibofsky.

DR. GIBOFSKY: No change from previous comments.

DR. WOOD: I would say the same as before but I would have a triple black-box warning and I would, again, offer the company the option to get back off probation if they can come up with clear and unequivocal safety data. Dr. Gross?

DR. GROSS: Same as Celebrex but I would make valdecoxib a second-line selective COX-2 inhibitor.

DR. HOLMBOE: I would contraindicate this drug for use in post-CABG surgery. I would strongly recommend banning it to consumer advertising and I clearly would make this a second-line drug.

DR. WOOD: Dr. Farrar?

DR. FARRAR: As opposed to what I said about Celebrex, I think I would provide in the black box an absolute contraindication in cardiac surgery, a contraindication stating that the long-term-use risk is unknown in the black box and that it is second-line with a clear indication that, if the company produces data obviating those, then those could be removed.

DR. WOOD: Dr. Manzi?

DR. MANZI: In addition to the Celebrex information I provided before, I agree with the contraindication in any revascularization procedure.

DR. WOOD: Dr. Hoffman?

DR. HOFFMAN: I would repeat the concerns I had about Celebrex in a black-box warning for this agent but, whereas I was not in favor of a duration limitation for Celebrex, I am in favor of a duration limitation for this agent for which we only have six-month data.

DR. WOOD: Dr. Dworkin?

DR. DWORKIN: For this agent, I would be in favor of a black-box warning and also stipulating that it should only be used third-line, I think, and then with the contraindications that other people have mentioned.

DR. WOOD: Dr. Boulware.

DR. BOULWARE: The same warning I had listed for the black box for celecoxib. I would also add a contraindication for CABG surgery and also a listing that we don't know the long-term use in cardiovascular risk.

DR. WOOD: Dr. Domanski.

DR. DOMANSKI: Number one, I am going to ask that I be allowed--I am given pangs of conscience by Dr. Nissen. I think he is right. I don't think the data are there and I would like to change my abstain to a no, if I am permitted to. With regard to the box, same as Celebrex but would add that it is contraindicated in the setting of post-bypass.

DR. WOOD: Dr. Fleming?

DR. FLEMING: I would add that it should be contraindicated in cardiac surgery. As I was thinking through this further, I was thinking there ought to be some mandated requirement, and we are going to get to this in Question 5, for trials that would give us the broader insight that we are lacking. I am troubled by the fact that when we look at the other four coxibs, they have all had, on average, 20,000 patients. We have three here. Dr. Nissen has persuaded me that we do need to be more forthcoming. We can't probably be as persuasive in mandating that as we can in voting no. So, with that logic, I would like to also change my abstain to a no.

DR. WOOD: Dr. Furberg.

DR. FURBERG: Same recommendation but I would add a limitation in use to 1 to 2 weeks mentioning in the black box or somewhere in the labeling that there is a lack of evidence for short- and long-term benefit and safety in low-risk patients.

DR. WOOD: Dr. Day?

DR. DAY: Same as before except the contraindications that others have mentioned and also no DTC.

DR. WOOD: Richard?

DR. PLATT: I would add a contraindication for patients undergoing cardiovascular surgery. Even though we will talk about additional trials later, I would make continued marketing of this drug conditional on an appropriately

designed randomized trial being undertaken forthwith.

DR. WOOD: Dr. Gardner?

DR. GARDNER: I will join my colleagues in converting from an abstain to a no and, therefore, not make recommendations for continued.

DR. WOOD: That was another change in the vote. Did you get that? You can see how hanging chads come; right? Dr. Gardner changed her vote from an abstain to a no. Dr. Elashoff?

DR. ELASHOFF: Elashoff. I would add a limitation to second-line therapy if this stays on the market.

DR. WOOD: Dr. Nissen?

DR. NISSEN: I would offer a stronger warning than we put on celecoxib which particularly emphasizes that longer-term safety has not been established and that the drug should not be used long-term until further data are forthcoming.

DR. GIBOFSKY: Excuse me. You said celecoxib; don't you mean-we are discussing valdecoxib.

DR. NISSEN: Similar to, similar warnings to, is what I said. So I wanted similar warnings but stronger with the proviso that we don't have the long-term safety data established and, therefore, the drug should not be used long-term.

DR. WOOD: Dr. Abramson?

DR. ABRAMSON: I would keep mine the same.

DR. WOOD: Let's take a break We will return at five past 3:00. That is ten minutes from now. And we will get started on the next question. (Break.)

DR. WOOD: Okay. Let's get started.

Question 2B: Valdecoxib: Clarification of Dr. Elashoff's vote

DR. WOOD: Dr. Elashoff's vote was not properly recorded because it was unclear what she said, apparently. Would she like to vote?

DR. ELASHOFF: I was told I had to say something other than "unclear," so I said no.

DR. WOOD: So you said no. That being the case, roll of the drum, the vote is 14 yes, 5 abstain and 12 no.

Question from Dr. Hennekens about Class Effect in CABG Patients

DR. HENNEKENS: Alastair, a point of information. I think we run the risk of giving a bad message here. If we are saying that valdecoxib is contraindicated in cardiac surgery patients when we haven't acknowledged that, if there really is a class effect, we wouldn't want doctors to get the mistaken impression that they should use another coxib or another NSAID instead of valdecoxib.

contraindicate all of them in cardiac surgery. Am I wrong about that, Dr. Temple? Dr. Jenkins?

DR. WOOD: I am assuming that the FDA will take that into account and

DR. JENKINS: That would certainly seem to be the logical conclusion since valdecoxib is only in oral dosage form and the others are oral as well.

DR. WOOD: So does that reassure you, Charlie? I know that someone said consistency is the hobgoblin of small minds, but I guess I have got one.

Question 2B: Valdecoxib Revote

DR. WOOD: Dr. Abramson, sorry. Could I interrupt you. The hanging chads have raised their head. They want to go back. We can't agree on the vote, apparently, for 2.b. So the question for 2.b. was, does the overall risk versus benefit profile for valdecoxib support

marketing in the U.S. Even though we announced the vote, and everybody rushed out to file the story, it was premature. We are going to have to retake the vote because we are not sure what the vote was, apparently. So, I have forgotten which side we started on now. Who started? Steve? Let's go around again and let me remind everybody what we are voting here. We are voting for

valdecoxib. Does the overall risk versus benefit profile for valdecoxib--we are going back to retake the vote for valdecoxib for Question 2.b. because there is some discrepancy, apparently, in the vote counting. Remember Florida? You thought I was kidding.

DR. NISSEN: Where is Katherine Harris now that we need her.

DR. WOOD: So we are going to go back and retake--isn't that right? We are going back to 2.b. We are going back to Question 2.b. and we are taking the vote on 2.b. The question is, for valdecoxib, Bextra, does the overall risk versus benefit profile for valdecoxib support marketing in the U.S. A yes would keep it on the market. A no would take it off the market. Steve are you--which one was it?

COMMITTEE MEMBER: Is it not on the tape recorder?

DR. ABRAMSON: Abramson. Yes.

DR. NISSEN: Nissen. Yes.

DR. ELASHOFF: Elashoff. No.

DR. GARDNER: Gardner. No.

DR. PLATT: Platt. Yes.

DR. DAY: Day, the hanging chad. I have to abstain because the question is based on the available evidence. That is the basis for my abstention.

DR. FURBERG: Furberg. No.

DR. FLEMING: Fleming. No.

DR. DOMANSKI: Domanski. No.

DR. BOULWARE: Boulware. Yes.

DR. DWORKIN: Dworkin. Yes.

DR. HOFFMAN: Hoffman. Yes, with restrictions on dose and duration.

DR. MANZI: Manzi. Yes.

DR. FARRAR: Farrar. Yes, with limitations on dose and duration.

DR. HOLMBOE: Holmboe. No.

DR. GROSS: Gross. No.

DR. WOOD: Wood. No.

DR. GIBOFISKY: Gibofsky. Yes.

DR. CRAWFORD: Crawford. No.

DR. CUSH: Cush. Yes.

DR. BATHON: Bathon. Yes. I had restrictions, also.

MS. MALONE: Malone. Yes.

MR. LEVIN: Levin. No.

DR. ILOWITE: Ilowite. I am one of the abstainers before. I will change it to yes.

DR. D'AGOSTINO: D'Agostino. I will balance that and change it to no.

DR. MORRIS: Morris. Yes.

DR. CANNON: Cannon. Yes. MS. SHAPIRO: Shapiro. No.

DR. PAGANINI: Paganini continues abstaining.

DR. FRIEDMAN: Friedman. I will go to
a no.

DR. HENNEKENS: Hennekens. Yes.

DR. SHAFER: Shafer. Yes.

Slide with Text of Question 2

Question 1, 2, 3

Do the available data support a conclusion that celecoxib, rofecoxib and valdecoxib significantly increase the risk of cardiovascular events?

Does the overall risk versus benefit profile for each of these support marketing in the US? If yes, please describe the patient population(s) in which the potential benefits of celecoxib outweigh the potential risks and what actions you recommend that FDA consider implementing to ensure safe use.

Committee Voting (in order of members voting) For Question 2C: POPULATIONS & RISK-MANAGEMENT WITH VALDECOXIB

Surname	1st Name	Expertise*	Member Comments
Abramson	Steven	Rheumatology	Same as for celecoxib.
Nissen	Steven	Cardiology	"stronger warning than we put on celecoxib which particularly emphasizes that longer-term safety has not been established and that the drug should not be used long-term until further data are available."
Elashoff	Janet	Statistics	"limitation to second-line therapy".
Gardner	Jacqueline	DSRMAC (Epidem.)	"I will join my colleagues in converting from an 'Abstain' to a 'No' and, therefore, not make recommendations for continued".
Platt	Richard	DSRMAC (Epidem.)	"contraindication for patients undergoing cardiovascular surgery", make "continued marketing of this drug conditional on an appropriately designed randomized trial being conducted first."
Day	Ruth	DSRMAC (Psychol.)	"contraindications that others have mentioned", "no DTC".
Furberg	Curt	Epidemiology	"limitation in use to 1 to 2 weeks", "mentioning in the black box or somewhere in the labeling that there is a lack of evidence for short- and long-term benefit and safety in low-risk patients."
Fleming	Thomas	Statistics	"contraindicated in cardiac surgery", "mandated requirement ... for trials that would give us the broader insight that we are lacking. I am troubled by the fact that when we look at the other four coxibs, they have all had, on average, 20,000 patients. We have three here. Dr. Nissen has persuaded me that we do need to be more forthcoming. We can't probably be as persuasive in mandating that as we can in voting no. So with that logic, I would like to also change my 'Abstain' to a 'No'."
Domanski	Michael	NIH Research	"Number one, I am going to ask that I be allowed--I am given pangs of conscience by Dr. Nissen. I think he is right. I don't think the data are there and I would like to change my abstain to a no, if I am permitted to. With regard to the box, same as Celebrex but would add that it is contraindicated in the setting of post-bypass."
Boulware	Dennis	Rheumatology	"contraindication for CABG surgery" and "listing that we don't know the long-term use in cardiovascular risk".
Dworkin	Robert	Anesthesiology	"black-box warning", "third-line" and "with the contraindications that other people have mentioned".
Hoffman	Gary	Rheumatology	"whereas I was not in favor of a duration limitation for Celebrex, I am in favor of a duration limitation for this agent for which we only have six-month data".
Manzi	Susan	Rheumatology	"contraindication in any revascularization procedure".
Farrar	John	Statistics	In the black box: "an absolute contraindication in cardiac surgery", "a contraindication stating that the long-term-use risk is unknown" and "second-line". Clear indication that, "if the company produces data obviating those, then those could be removed."
Holmboe	Eric	DSRMAC	"contraindicate this drug for use in post-CABG surgery". Ban for "consumer advertising". "I clearly would make this a second-line drug".
Gross	Peter	DSRMAC	"make valdecoxib a second-line selective COX-2 inhibitor".
Wood	Alastair	Pharmacology	"triple black-box warning".
Gibovsky	Alan	Rheumatology	Same as for celecoxib.
Crawford	Stephanie	DSRMAC (Pharmacy)	Same as for celecoxib.
Cush	John	Rheumatology	"change the warning to a black box regarding CABG and any other acute cardiac situation".
Bathon	Joan	Rheumatology	"black-box warning for this drug with the advisory about the CABG patients and against chronic use until further safety data are available in the target populations".
Malone	Leona	Patient Representative	"emphasize the need for postmarketing surveillance"
Levin	Arthur	DSRMAC (Consumer)	Same as for celecoxib.
Ilowite	Norman	Rheumatology	"discussion of the CABG data"
D'Agostino	Ralph	Statistics	Same as for celecoxib.
Morris	Louis	DSRMAC	"I would suggest a medication guide. I would also suggest a contraindication that would be both in the contraindications section and the black box in cardiac surgery. I would also try to develop some kind of special program that would be coordinated with patients undergoing cardiac surgery that would have some kind of extra warning."
Cannon	Richard	NIH Research	Same as for celecoxib.
Shapiro	Robyn	DSRMAC (Ethicist)	"exclude its use ever in post-cardiac surgery".
Paganini	Emil	Nephrologist	"alter the black box to include only post-cardiac surgery"
Friedman	Lawrence	NIH Research	Same as for celecoxib.
Hennekens	Charles	Epidemiology	Same as for celecoxib.
Shafer	Steven	Anesthesiology	"in anesthesia, we do desperately need better options in the immediate post-operative period for which the intravenous form is an intriguing opportunity".