

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 225 recommendations (an average of 7/member) for action

(“Yes”), and 20 disagreements with prior recommendations by others (“No”). The categories and “Yes vs. No” tabulations were as follows:

Net Count (Yes - No)	Category
22	1. Black-box warning (25 vs 3)
17	2. Patient Medication Guide (18 vs 1)
16	3. High dose contraindicated (17 vs. 1)
16	4. Contraindicated in cardiovascular surgery (16 vs 0)
15	5. Ban Direct To Consumer Adverts (19 vs 4)
11	6. Warning for High Dosage (11 vs 0)
9	7. Patient Consent/Attestation (10 vs 1)
8	8. Warning of Increase in Blood Pressure (8 vs 0)
7	9. Warning for Long Duration (7 vs 0)
7	10. Second Line Drug (12 vs 5)
6	11. Warning for High Cardiovascular Risk (6 vs 0)
6	12. Easier-To-Understand Explanation of Risk (6 vs 0)
6	13. Postmarketing studies (6 vs 0)
5	14. Same labeling for NSAIDs (5 vs 0)
5	15. Allow Black-box Removal if Adequate Trials Performed (5 vs 0)
5	16. Patient Registry (5 vs 0)
3	17. Long Duration of Therapy Contraindicated (5 vs 2)
3	18. Don't use in adults (3 vs 0)
2	19. Exclude if at High Cardiovascular Risk (4 vs 2)
2	20. Academic Detailing (2 vs 0)
2	21. Educate Healthcare Professionals (2 vs 0)
2	22. Assess/manage cardiovascular risk (2 vs 0)
2	23. Marketing contingent on LT study forthwith (2 vs 0)
2	24. Insufficient data on LT risk (2 vs 0)
2	25. Third-Line drug (2 vs 0)
1	26. Dear Healthcare Professional Letter (1 vs 0)
1	27. OTC Restrictions (1 vs 0)
1	28. Define “class” (1 vs 0)
1	29. Define mechanism (1 vs 0)
1	30. Comprehension survey for patient consent (1 vs 0)
1	31. FDA study of patient medication guides (1 vs 0)
1	32. Aspirin May Not Reduce CV Risk and May Increase GI Risk (1 vs 0)
1	33. Combined analysis of COX-2 & Framingham data (1 vs 0)
1	34. Do ALLHAT-Type Study (1 vs 0)
1	35. Warn of Risk of Short-acting NSAIDs (1 vs 0)
1	36. Warn of Risk of COX-2 selective traditional NSAIDs (1 vs 0)
1	37. Lack of Safety Data in Long-Term patients (1 vs 0)
1	38. Special program to prevent use in Cardiac Surgery (1 vs 0)
1	39. Contraindicated in ANY revascularization procedure (1 vs 0)
1	40. Reexamine pediatric dosage (1 vs 0)
1	41. Study blood pressure and atherogenesis in children (1 vs 0)
1	42. Reminder every 6-12 months of LT therapy (1 vs 0)
1	43. Mention risk of heart failure (1 vs 0)
1	44. Mention lack of data on cardiovascular effects in children (1 vs 0)
0	45. Say that Naproxen is Safer than Coxibs (1 vs. 1)
	Other (3)

Question 3A: Discussion: Increased risk of CV events with rofecoxib

- Dr. Ilowite wanted to “remind everybody” that rofecoxib is the only COX2 inhibitor that is approved for juvenile rheumatoid arthritis, and also that it is available as a liquid.

Question 3A: Voting: Increased risk of CV events with rofecoxib

- The voting was 32 to 0.
- There were no additional comments other than from Dr. Elashoff who said “Yes. Both against placebo and against naproxen”.

Question 3B: Discussion: Support for marketing of rofecoxib

- **ROFECOXIB & CELECOXIB HAVE SIMILAR RISK VS. PLACEBO:** Dr. Hennekens said that the point estimate for risk of rofecoxib versus placebo is “practically identical to that for celecoxib.” The “discrepancy” only occurs when naproxen was used as a comparator in rofecoxib trials.
- **BLOOD PRESSURE EFFECT MORE WITH ROFECOXIB:** Dr. Nissen said, “however”, the blood pressure effects of rofecoxib “are clearly outside of other drugs in the class including celecoxib...” and “a 5- or 6-millimeter average blood-pressure increase over a period of time is very undesirable since there are other drugs in the NSAID and coxib class that do not appear to have that very large signal on blood pressure”. He was also concerned about the “heart-failure signal” with rofecoxib compared to “the APC and approved trials. What you see is almost no heart-failure events”. Dr. Hennekens asked why, in view of what Dr. Nissen said, the APTC cardiovascular index did not show “a higher risk estimate”. Dr. Nissen said “there may be a latency issue here” and “it takes a while for hypertension to yield an excess of events”.
- **VERY LARGE EARLY HEART FAILURE RISK: ROFECOXIB WORSE THAN OTHERS?** Dr. Wood said that “the data here are very compelling” with the “cardiovascular risk in the APPROVe trial” and “the very large risk from heart failure which separates very early”. “So there is a clear signal this drug appears substantially worse than the others. I can’t see any reason to keep it on the market.” Dr. Furberg disagreed with these heart failure conclusions and said that celecoxib versus placebo had a risk ratio of 6 as compared with a risk ratio of 4 in the rofecoxib APPROVe trial.

- **STRONG DOSE-RESPONSE FOR ROFECOXIB SAFETY SIGNAL:** Dr. Paganini said that rofecoxib had a “much stronger dose relationship” than the other coxibs with 50 mg “probably not very good”, 25 mg “a little better” and 12.5 mg “back to where the other NSAIDs seemed to be”.
- **ADVANTAGES OF ROFECOXIB:** Dr. Manzi commented that not only is rofecoxib “the only drug approved for “juvenile rheumatoid arthritis “as Dr. Ilowite pointed out”, but it is the “only one with a G.I. safety proven indication”, and because of its once-daily dosing has favorable patient compliance. Dr. Bathon said that rofecoxib was the only coxib available for those who are sulfa-allergic.
- **IS ROFECOXIB TOXICITY RELATED TO LONG HALF-LIFE?** Dr. Wood suggested that the once-daily dosing might contribute to the cardiovascular toxicity of rofecoxib.
- **ALL 3 LT STUDIES HAVE SAFETY PROBLEM:** Dr. Fleming said that each of the three long-term rofecoxib trials had a safety problem: cardiovascular events in APPROVe and VIGOR, and increased mortality in the Alzheimer’s trial.

Question 3B: Voting: Support for marketing of rofecoxib

DR. SHAFER: No. (“overwhelmingly no, although if individual patients can petition the company under some mechanism, I would support that”).

DR. HENNEKENS: Yes.

DR. FRIEDMAN: No.

DR. PAGANINI: Yes.

DR. SHAPIRO: No.

DR. CANNON: No.

DR. MORRIS: Yes “but”.

DR. D'AGOSTINO: No.

DR. ILOWITE: Yes.

MR. LEVIN: No.

MS. MALONE: Yes. “with reservation”.

DR. BATHON: Yes. “but at lower dose, no 50 milligrams”.

DR. CUSH: Yes.

DR. CRAWFORD: Yes.

DR. GIBOFSKY: Yes.

DR. WOOD: No.

DR. GROSS: No.

DR. HOLMBOE: Yes. “but only for children”.

DR. FARRAR: Yes.

DR. MANZI: Yes.

DR. HOFFMAN: No.

DR. DWORKIN: Yes. “with restrictions”.

DR. BOULWARE: Yes.

DR. DOMANSKI: No.

DR. FLEMING: No.

DR. FURBERG: No.

DR. DAY: No.

DR. PLATT: Yes.

DR. GARDNER: Yes. “with restrictions”.

DR. ELASHOFF: No.

DR. NISSEN: No. “but with a possible compassionate-use program”.

DR. ABRAMSON: Yes.

Question 3C: General Discussion: Risk-management and suitable populations for Rofecoxib

- **JRA PATIENTS HAVE LOW CV RISK:** Dr. Holmboe said that rofecoxib’s indication in juvenile rheumatoid arthritis applies to a population at “very low cardiovascular risk”.
- **HYPERTENSION & EDEMA COMMON TO CLASS: MONITORING NEEDED:** Dr. Farrar suggested that the risk of hypertension and edema is shared with the other drugs, so that there should be monitoring for these events as well as a “more formal warning” as effects might otherwise not be noted in a “young, healthy person”.
- **TOP DOSE AND LONG DURATION UNACCEPTABLE:** Dr. Morris said that the highest dose of rofecoxib should be removed from the market and “really bold warning” is needed on “duration of use”. Dr. Paganini agreed.
- **HYPERTENSION AND DOSE-RESPONSE OF CONCERN:** Dr. Abramson said the concern with rofecoxib is hypertension and the dose-response and the maximum dose should be addressed.
- **BLOOD PRESSURE CONCERN IN CHILDREN:** Dr. Hoffman said that he was concerned about even slight increases in blood pressure in chronic use in children. Dr. Nissen said that blood pressure is a “continuous risk factor”, that the increase in blood pressure occurs even with the 25 mg rofecoxib dose, and there is no reason to suppose that other agents could not be developed for juvenile rheumatoid arthritis.
- **CHANGE IN BP ON STOPPING ROFECOXIB NOT KNOWN:** Dr. Morris asked what happens to the blood pressure when patients are taken off rofecoxib. Dr. Nissen believed “that it would be likely, at

least in large part reversible, but I am not sure anyone has such data”.

- **DO BP AND ATHEROGENESIS STUDIES IN CHILDREN:** Dr. Ilowite suggested that approval in children could be made contingent of long term blood pressure and atherogenesis effects. Dr. Nissen said this would be difficult to study because of the long latency for events to occur. Dr. Ilowite said that blood pressure should be “easy to study” and other trials use “surrogate early markers of atherosclerosis”. Dr. Farrar mentioned that the NIH is getting “a billion dollars worth of money to study pediatric diseases” and they might be persuaded to look at these issues.
- **NO BP CHANGES IN ROFECOXIB JRA TRIALS:** Dr. Manzi asked if there were blood pressure changes in the rofecoxib JRA trials. Dr. Ilowite said there were no such issues.
- **CAN ROFECOXIB-INDUCED HYPERTENSION BE “MANAGED”?** Dr. Temple said that blood pressure “is something we

ordinarily think of as treatable” and asked if rofecoxib’s effect on blood pressure could be managed. Dr. Wood and Dr. Nissen pointed out that blood pressure was managed in APPROVe and there was more use of anti-hypertensive drugs, but the blood pressure was still higher and there were increased dropouts because of hypertension. Dr. Nissen said that, in addition, “treated hypertension still confers a risk over no hypertension”; Dr. D’Agostino agreed, based on the Framingham data.

- **HIGHER ROFECOXIB DOSES MAY BE MORE EFFECTIVE AND MORE TOXIC:** Dr. Hennekens (during 3C voting) said “I share Steve's concern that blood pressure is a greater potential issue here but Richard's that it is likely that higher doses of this drug lead to greater benefits. This may offer one plausible explanation for the higher risk seen in observational studies.

Question 3C: Around-the-table comments by committee: Risk-management and suitable populations for Rofecoxib

DR. ABRAMSON:

“stronger label in terms of hypertension and potential cardiovascular outcomes”,

“restriction of upper dose to be determined”,

“leave open the possibility of some change of this with future studies”,

“second choice” drug.

DR. NISSEN:

Restrict dose to 12.5 mg “if anything is done with the drug),

“I don't want to go there. But, if we do go there, I would put the most difficult and most complex warning on there possible”.

DR. ELASHOFF:

“Stronger than either of the two previous cases”.

DR. GARDNER:

“Stronger”,

“register patients or otherwise bring attestation into the risk-management program”,

“good, strong postmarketing” evaluation.

DR. PLATT:

“dose restriction”.

DR. DAY:

“More restriction”.

DR. FURBERG:

“Stronger black-box warnings”.

DR. FLEMING:

“same conditions and concerns that Steve Nissen indicated”.

DR. DOMANSKI:

“underscore second-line drug”.

DR. BOULWARE:

Same as for celecoxib.

DR. DWORKIN:

“third-line” drug

“a patient will have had to have failed two NSAIDs, whether selective or not, before they try this drug.”

DR. HOFFMAN:

“restriction in dose to 12.5 mg”.

DR. MANZI:

“restrict only the 50-milligram dose”,

“have patient consent” better than not having the drug available.

DR. FARRAR:

“strong black-box warning including an indication of ongoing monitoring of blood pressure in all patients including children”,

“I am conflicted about the idea of registration”,

“some sort of patient consent”,

“restriction in dose”.

DR. HOLMBOE:

“I agree with what has been said previously”,

if used in adults “there should be some sort of informed-consent process”.

DR. GROSS:

“strong black-box warning”,

“second-line drug”,

“restricted to 12.5 mg dose”.

DR. WOOD:

“black-box warning”,

“very restricted access program”,

“attestation and some clear ability of patients to consent”,

“be careful not to” put children “at even greater risk with their lifelong hypertension risk, their lifelong exposure to cardiovascular risk factor”.

DR. GIBOFSKY:

restrict dose to 12.5 mg “for chronic use, not for acute use”,

“very strong black-box warning to emphasize the hypertension, cardiovascular, at the higher dose”,

“second or third choice”,

consider “Subpart H where there would be very strong restrictions on who would have access to it”.

DR. CRAWFORD:

“stronger black-box warning”,

“dose limits as appropriate”,

“duration limits”,

“second-line”

“informed consent”.

DR. CUSH:

“removal of the 50-milligram dose from the market”,

“black-box warning”.

DR. BATHON:

“strong black-box warning”,

“elimination of the 50 mg” dose,

“second choice”.

MS. MALONE:

“ongoing studies”,

“patient consent”,

MR. LEVIN:

“Black-box warnings”,

“I am intrigued by the notion of a Subpart H approach”.

DR. ILOWITE:

“strong black-box warning”,

“elimination of the 50 mg dose”,

“reexamination of the dose in children”,

“studies of blood pressure and atherogenesis”.

DR. D'AGOSTINO:

“Stronger black-box warning”,

“dose restriction to 12.5” mg,

“restricted access”.

DR. MORRIS:

“Black box”,

“withdrawal of the highest dose”,

patient “consent”,

“reminder sent to the patient about either six months or a year, depending upon issues related to duration to remind them about the risks of long-term use”.

DR. CANNON:

“strong black-box warning”,

“no direct-to-consumer advertising”,

limit use “to a short-term use for pain in adults and for chronic use in children and young adults with JRA with careful monitoring of blood pressure”.

DR. SHAPIRO:

“I agree with what Dr. Cannon just said”,

“some dose limitations”.

DR. PAGANINI:

“Black box to include very strong and severe dose and time restrictions as well as cardiovascular”,

“spell out the cardiovascular clearly to include blood pressure and congestive heart failure”,

“no direct advertising”,

“move from a patient brochure as a patient consent”.

DR. FRIEDMAN:

“elimination of the high 50” mg dose.

DR. HENNEKENS:

“global risk assessment and aggressive management of cardiovascular risk”,

DR. SHAFER:

“If it is to be marketed, I think it should only be indicated for children not adequately treated with conventional NSAIDs”,

“The black-box warning should state that the cardiovascular effects in children are unknown and that the use in adults is not recommended”,

“The adult use should be limited to compassionate use only which, I believe, is the Subpart H restriction”.

Discussion Text: Question No. 3: Rofecoxib

Introduction

DR. WOOD: We are going to move on to Question No. 3. I think we have got the system down pat now. We know what we are doing here, hopefully. The

first question is, do the available data support a conclusion that rofecoxib significantly increases the risk of cardiovascular events. We have been over this a lot, I think, so we probably don't need a lot of discussion. But I will

entertain discussion if there is any. Seeing no hands, we will-which side did we start on last time? Over here. Yes, Dr. Ilowite.

DR. ILOWITE: Just to remind everybody that this is the only celecoxib that has been approved for JRA and was available as a liquid.

DR. WOOD: Can we just hold for a moment.

Question 3A

DR. WOOD: Let's move on, then. Which side did we start on last time. I have forgotten. You started last time? All right. Let's start with Dr. Abramson. Do the available data support a conclusion that rofecoxib significantly increases the risk of cardiovascular events.

DR. ABRAMSON: Yes.

DR. NISSEN: Nissen. Yes.

DR. WOOD: Hang on. I have been asked to ask each of you to give your name before you give the vote. Sorry. So, Dr. Abramson?

DR. ABRAMSON: Abramson. Yes.

DR. WOOD: Nissen?

DR. NISSEN: Nissen. Yes.

DR. ELASHOFF: Elashoff. Yes. Both against placebo and against naproxen.

DR. GARDNER: Gardner. Yes.

DR. GARDNER: Would you say that again. I didn't hear what you said.

DR. ILOWITE: We are talking about Question 3; right?

DR. WOOD: Right.

DR. ILOWITE: I was just going to remind everybody, this is the only COX-2 inhibitor that has been approved for treatment of juvenile rheumatoid arthritis and was available as a liquid.

DR. PLATT: Platt. Yes.

DR. DAY: Day. Yes.

DR. FURBERG: Furberg. Yes.

DR. FLEMING: Fleming. Yes.

DR. BOULWARE: Boulware. Yes.

DR. DWORKIN: Dworkin. Yes.

DR. HOFFMAN: Hoffman. Yes.

DR. MANZI: Manzi. Yes.

DR. FARRAR: Farrar. Yes.

DR. HOLMBOE: Holmboe. Yes.

DR. WOOD: Wood. Yes.

DR. GIBOFSKY: Gibofsky. Yes.

DR. CRAWFORD: Crawford. Yes.

DR. CUSH: Cush. Yes.

DR. BATHON: Bathon. Yes.

MS. MALONE: Malone. Yes.

MR. LEVIN: Levin. Yes.

DR. ILOWITE: Ilowite. Yes.

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

DR. MORRIS: Morris. Yes.

DR. CANNON: Cannon. Yes.

DR. SHAPIRO: Shapiro. Yes.

DR. PAGANINI: Paganini. Yes.

DR. FRIEDMAN: Friedman. Yes.

DR. HENNEKENS: Hennekens. Yes.

DR. SHAFER: Shafer. Yes.

DR. WOOD: Dr. Gross has returned.

DR. GROSS: Yes.

DR. WOOD: Dr. Domanski has returned. The question we are voting on is, does the available data support a conclusion that rofecoxib significantly increases the risk of cardiovascular events.

DR. DOMANSKI: Yes.

Voting Results for Question 3A

DR. WOOD: Okay. The vote is 32 yes.

Question 3B Discussion

Let's move on to the next question; does the overall risk versus benefit profile for rofecoxib support marketing in the U.S. We will start with--do you want discussion on that first?

DR. HENNEKENS: Yes.

DR. WOOD: All right. Charlie.

DR. HENNEKENS: I think it is important to point out that, in the placebo-controlled trials, the point estimates for rofecoxib are practically identical to that for celecoxib. Where there appears to be a discrepancy is the

rofecoxib trials use naproxen as a comparator which always compares favorably. Some of the celecoxib trials use the short-acting NSAIDs which I continue to believe has been an issue that we, I know, will discuss. But I think the overall placebo-controlled comparisons are pretty much identical to one another.

DR. WOOD: Any other discussion? Dr. Nissen?

DR. NISSEN: There are some troubling things, however. If you look at all the evidence including the meta-analysis,

the blood-pressure effects for the drug are clearly outside of other drugs in the class including celecoxib and so on. So one of the things that troubles me is I happen to think that the prostacyclin factor is not the only one. I share Bob Temple's concern that a 5- or 6-millimeter average blood-pressure increase over a period of time is very undesirable since there are other drugs in the NSAID and coxib class that do not appear to have that very large signal on blood pressure. There is another signal here as well that I think it is important that we understand and that is the heart-failure signal. Compare the heart-failure events in the APC and approved trials. What you see is almost no heart-failure events. Now, you don't know if they are the same definitions, but you would like to believe they are. And you see this pulmonary edema, heart failure, very, very strong signal, as evidenced by the Kaplan Meier curve that was in the New England Journal of Medicine. So I think there are differences within the class. I think the problem emerges much more clearly with rofecoxib, particularly on the blood-pressure, heart-failure, side. So my thinking is that there are safer alternatives and, therefore, it isn't the same. It isn't identical.

DR. HENNEKENS: A quick question on that. If you think there is more hypertension and heart failure, then in the APT collaboration events of non-fatal M.I., non-fatal stroke and vascular death, in the placebo-controlled trials, why doesn't that added hazard translate into a higher risk estimate?

DR. NISSEN: What you are saying is heart failure and edema don't immediately translate to thrombotic events.

DR. HENNEKENS: No; but blood pressure does on stroke and on M.I.

DR. NISSEN: There is a latency, of course. It takes a while for hypertension to yield an excess of events. So there may be some latency issues here as well. But I do think the signal on blood pressure is different for this age. I think, you know, if you look at the data dispassionately, you come to that conclusion. So it makes me more concerned.

DR. WOOD: I also have a view on this. I think the data here are very compelling. There are two trials, as Steve just said. There is not only the cardiovascular risk in the APPROVe trial, there is also the very large risk from heart failure which separates very early. So there is a clear signal this drug appears substantially worse than the others. I can't see any reason to keep it on the market. Curt?

DR. FURBERG: I don't think that is correct for heart failure. In the placebo-controlled trials of Celebrex had a risk ratio of 6. The risk ratio in the APPROVe study was 4. So there is no indication that Vioxx is worse than Celebrex for causing heart failure.

DR. WOOD: Dr. Paganini.

DR. PAGANINI: I think this drug really has a much stronger dose relationship than the others have. I think if you take a look at the doses, at the higher doses, you get a much higher response. The studies showed clearly that 50 milligrams is probably not very good, 25 a little bit better, but 12-and-a-half came back to where the other NSAIDs seemed to be. So I would sort of strongly look at dose response in this particular drug

versus the others. I think it is much more apparent here than the others.

DR. WOOD: Dr. Shafer. No? Any other comments? Sorry, Dr. Manzi. It is hard to see over in this corner.

DR. MANZI: I just wanted to point out in the interest of a risk:benefit way, number one, that, as Dr. Ilowite pointed out, this is the only drug approved for pediatrics, for JRA, too. It is the only one with a G.I. safety proven indication. Other than its efficacy, I would also point out that the once-day dosing, whether it be 25 milligrams or whatever, has been a very favorable component for patients as far as compliance issues.

DR. WOOD: Of course, it might be related to its toxicity, even, the once-day dosing. Any other comments?

DR. BATHON: It is also the only drug available that can be used in people who are sulfa-allergic.

DR. WOOD: Was there somebody else? Dr. Fleming?

DR. FLEMING: In addition to the excesses that are strongly seen in the VIGOR and the APPROVe trial, the APPROVe trial, Charlie, is placebo-controlled so maybe I missed the essence of what you were saying. The APPROVe trial does show a substantial increase in a placebo-controlled setting and also shows, in that context, that the excesses are cardiac events as well as cerebrovascular events. The most favorable of these is the Alzheimer's study if you are just looking at cardiovascular events and yet, that is the study--if that is our positive study, that is the study that shows a statistically significant increase in mortality at 41 against 23. So we have got some significant concerns in each of the trials. Even with the trial that is favorable, or neutral is a better term, in terms of the cardiovascular events, is very unfavorable in mortality.

Question 3B Voting

DR. WOOD: Are we ready to go around the room? I think so. We would like to start with Dr. Abramson. I'm sorry. Dr. Shafer.

DR. SHAFER: I would say overwhelmingly no, although if individual patients can petition the company under some mechanism, I would support that.

DR. WOOD: Dr. Hennekens.

DR. HENNEKENS: Hennekens. Yes.

DR. FRIEDMAN: Friedman. No.

DR. PAGANINI: Paganini. Yes. MS.
SHAPIRO: Shapiro. No.

DR. CANNON: Cannon. No.

DR. MORRIS: Morris. Yes, but.

DR. D'AGOSTINO: D'Agostino. No.

DR. ILOWITE: Ilowite. Yes.

MR. LEVIN: Levin. No.

MS. MALONE: Malone. Yes, with reservation.

DR. BATHON: Bathon. Yes, but at lower dose, 50 milligrams. (TMT Note: Transcript is in error here – Dr. Bathon said “no 50 milligrams”)

DR. CUSH: Cush. Yes.

DR. CRAWFORD: Crawford. Yes.

DR. GIBOFSKY: Gibofsky. Yes.

DR. WOOD: Wood. No.

DR. GROSS: Gross. No.

DR. HOLMBOE: Holmboe. Yes, but only for children.

DR. FARRAR: Farrar. Yes.

DR. MANZI: Manzi. Yes.

DR. HOFFMAN: Hoffman. No.

DR. DWORKIN: Dworkin. Yes, with restrictions.

DR. BOULWARE: Boulware. Yes.

DR. DOMANSKI: Domanski. No.

DR. FLEMING: Fleming. No.

DR. FURBERG: Furberg. No.

DR. DAY: Day. No.

DR. PLATT: Platt. Yes.

DR. GARDNER: Gardner. Yes, with restrictions.

DR. ELASHOFF: Elashoff. No.

DR. NISSEN: Nissen. No, but with a possible compassionate-use program.

DR. ABRAMSON: Abramson. Yes.

Question 3C Discussion (1)

DR. WOOD: Okay. While we are doing our counting, let's go on and review the restrictions we would want to have on this if it were on the market. This time, we will start with Dr. Abramson.

DR. ABRAMSON: I think the concern with rofecoxib is the dose response and the hypertension. I think there should be some addressing of the maximum dose—

<Discussion interrupted for retaking of valdecoxib 2B vote>

Question 3 C Discussion (2)

DR. WOOD: While we are waiting, is there discussion on 3.c.? 3.c. is what we would done in terms of restrictions were rofecoxib to come back on the market. Is there someone else that could do the count if we could vote? I beg your pardon. Go ahead.

DR. HOLMBOE: I just wanted to make a comment that it sounds like Vioxx is really the only thing that is available for pediatric JRA. Since our major concern is cardiovascular risk, I am persuaded by the arguments that you have made that I would hate to remove something that may be of benefit to a population likely to be at very low cardiovascular risk.

DR. WOOD: But we could keep it on the market just for JRA if we wanted. All other drugs could get approval for that, I guess. So that is your comment. Any other comments? Sorry; Dr. Farrar?

DR. FARRAR: A comment about thinking about these drugs in general which is that, although hypertension risk and the edema risk may be higher in terms of the studies that we have looked at, they clearly occur with the other drugs in this category. In fact, a part of the labeling of the drugs ought to be recommendations about monitoring for those issues. I think, in this particular case, perhaps one of the restrictions would be added to some more formal warning. But I think the point is that, even a low risk of increased hypertension which may go unnoticed in a young, healthy person, would be an important criteria for long-term use of any of these drugs and clearly for this one.

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

DR. MORRIS: This is a case where, even though I am in favor of the marketing of the drug, I am not in favor of the marketing of the highest dose. I think that should be removed from marketing. I also would very heavily support some kind of really bold warning on duration of use for this drug as well.

DR. WOOD: Dr. Paganini.

DR. PAGANINI: I would second those sentiments.

DR. WOOD: Dr. Hoffman?

DR. HOFFMAN: I am concerned about the pediatric issue for two reasons, one, that Norm Ilowite stated in regards to lack of a lot of other options, but also the concern about silent, insidiously progressive, cardiovascular injury. I would be very interested in Dr. Nissen's comments even though they may be entire theoretical about what we might be buying into in approving this for chronic use in children.

DR. WOOD: Okay. Let's--

DR. PLATT: One more.

DR. WOOD: Okay. Dr. Platt first and then Dr. Nissen.

DR. PLATT: It seems to me, to the extent that we believe there are differences between drugs in this class, that rofecoxib is the extreme, both in

terms of its potential danger and its potential benefit. So I think that the onus on informed choice is greater for this drug than for the others.

DR. WOOD: Dr. Nissen?

DR. NISSEN: I am concerned. Part of it comes from a long history of studies with blood pressure that show that it is a continuous risk factor. It extends really way down into the normal range and part of the reason why I was arguing against bringing the drug back is that, while it may be true that it is the only drug approved for JRA, there is not any reason to believe that other agents could not, in fact, be developed for use in that population. I am worried that, if you increase blood pressure 5 or 6 millimeters of mercury over a long period of time, you will have a very adverse effect on the health of individuals. So, because I believe the blood pressure is such an important surrogate endpoint in cardiovascular risk, it puts the rofecoxib data in a different perspective. I guess the other thing I want to make sure everybody understands, is that there are some differences in what was seen. The dose that was used and approved was the 25-milligram dose, not the 50-milligram dose. There is a very, very strong signal there. That kind of signal is only seen at 800 milligrams in the APC trial. So I think that there is a much greater effect here with this agent even at doses that are not supra-therapeutic. So, if we do bring the drug back, I think that the 12-and-a-half-milligram dose is the only dose that I would be comfortable with because we have seen a pretty strong signal at 25. If you recall, we haven't seen signals at 200 for celecoxib. So it is quantitatively and qualitatively quite a

different signal with rofecoxib than celecoxib. So I just hope everybody understands the implications of a decision to put this drug back on the market.

DR. MORRIS: What is the effect, if blood pressure is raised, like you say, for, let's say six months, what is the effect if someone is taken off the drug? Does that effect go on or does blood pressure return to normal? Do we know?

DR. NISSEN: I don't have any data to that effect. I would believe that it would be likely, at least in large part reversible, but I am not sure anyone has such data.

DR. WOOD: Dr. Ilowite?

DR. ILOWITE: So, if there were a way to make approval in children contingent upon further study on effects on blood pressure and other mechanisms of atherogenesis that might have long-term use, I would certainly be in favor of that.

DR. NISSEN: It is pretty difficult to study because the latency--you know, if you are going to say, well, I am going to increase the life-long risk of cardiovascular disease in a young person, you are going to have to wait a long time and do an awful big study to see it. So it is just not a studyable phenomenon. You have to accept the importance of blood pressure as a surrogate measure and make the decision on that basis.

DR. ILOWITE: If I could just comment. Certainly, blood pressure, which would be easy to study. Secondly, there are trials in existence now looking at surrogate early markers of atherosclerosis in adolescents and older

children, not pre-adolescents, that might be useful.

DR. WOOD: That was Dr. Ilowite again. Are we ready to take a vote?

DR. FARRAR: One more.

DR. WOOD: Sorry, Dr. Farrar.

DR. FARRAR: This is Dr. Farrar. It actually is a very opportune time to think about this kind of long-term study. As many of you know, the NIH is in the process of putting together approximately a billion dollars worth of money to study pediatric diseases. Perhaps, the advice of this committee could be used to sway them in terms of looking at those issues.

DR. WOOD: Dr. Manzi?

DR. MANZI: I just had a question because we didn't have, really, access to the data in JRA as far as efficacy with Vioxx. Were there blood-pressure issues in those trials?

DR. ILOWITE: There were no blood-pressure issues to my knowledge. I think it was a study against naproxen and showing--

DR. WOOD: Do we know there were no blood-pressure issues, or do we just not know?

DR. ILOWITE: I would know if there were blood-pressure issues.

DR. WOOD: Bob, do you know?

DR. TEMPLE: No; I don't know. But what I wanted to ask Steve was whether

he thought seeing whether you could manage the blood pressure and how you could manage the blood pressure would be of interest. Blood pressure is something we ordinarily think of as treatable.

DR. WOOD: It was managed in APPROVe, though, wasn't it? And you still ended up with a higher blood pressure. I forget the data now. Steve, isn't that right?

DR. NISSEN: Yes. What was observed was there was a blood-pressure differential. But, in addition, there was a greater use of antihypertensive agents.

DR. WOOD: There was a greater dropout because of hypertension, too.

DR. NISSEN: One of the problems is that if you actually look at the data very, very carefully and maybe Ralph may be able to comment on this, that treated hypertension still confers a risk over no hypertension; that is to say, bringing the blood pressure down to the same level with a drug does not neutralize the risk of hypertension in all the epidemiological--

DR. D'AGOSTINO: Certainly, the Framingham data says that. You have a 160 systolic on treatment, you are at higher risk than a 160 systolic natural.

DR. NISSEN: That's right.

DR. D'AGOSTINO: You are presumably coming down from a much higher level and pulling it down. But it definitely does not restore you. You have to bring it down to something like 120 where you don't see a difference.

Question 3C Discussion (3): Round The Table:

DR. WOOD: Okay. Let's go around the room starting with Dr. Abramson.

DR. ABRAMSON: On 3.c.?

DR. WOOD: We are on 3.c. I guess, again, the issue is: Are there incremental changes you want to make over your previous votes here?.

DR. ABRAMSON: I think this is a tougher one and Dr. Nissen articulated the concerns. So I would have a stronger label in terms of hypertension and potential cardiovascular outcomes. I would have a restriction of upper dose to be determined. And I would leave open the possibility of some change of this with future studies. This is one drug, based on the evidence right now, that I might make a second choice if I had to-- given the evidence that we have.

DR. NISSEN: Because we have evidence both at 25 and 50 milligrams that is really quite robust, if anything is done with the drug, it should be at a dose of 12-and-a-half. Again, I am concerned. I would also just want to make sure everybody understands that if you look at all the observational studies, this was the outlier. So, if you really want to make this evidence-based, you have got to look at all the evidence. You have got two trials and observational data that are telling you the same thing, that this is not a safe alternative. So I don't want to go there. But, if we do go there, I would put the most difficult and most complex warning on there possible.

DR. ELASHOFF: Elashoff. Stronger than either of the two previous cases.

DR. GARDNER: Gardner. Stronger as well. This may be the drug that we ask to register patients or otherwise bring attestation into the risk-management program as well as a good, strong postmarketing or continued marketing ongoing evaluation.

DR. PLATT: Platt. I started off at the extreme with the other drugs. So I stay there, though I would add the dose restriction for this drug.

DR. DAY: More restriction, except I must say, were they unlucky that they used higher doses to begin with? They were the first one that entered, as I recall, the marketing fray.

DR. WOOD: No, no.

DR. DAY: Oh; that's right. So, if they had come in at 12-and-a-half and 25, it might have been different. But, okay; more restrictions, if it were to come back.

DR. FURBERG: Furberg. Stronger black-box warnings.

DR. FLEMING: Fleming. I would add the same conditions and concerns that Steve Nissen indicated.

DR. DOMANSKI: Domanski. I would use the same recommendations I did for Celebrex. I would underscore second-line drug.

DR. BOULWARE: I have nothing further to add. Boulware.

DR. DWORKIN: I agree with what has been said. I would actually think about making this third-line, but a patient will have had to have failed two NSAIDs, whether selective or not, before they try this drug.

DR. HOFFMAN: Hoffman. I agree with the black-box warning should this be remarketed with restriction in dose to 12.5 milligrams.

DR. MANZI: I agree with the black-box label. I would restrict only the 50-milligram dose. If there were a choice, I would rather have patient consent versus not having the drug available.

DR. FARRAR: John Farrar. A strong black-box warning including an indication of ongoing monitoring of blood pressure in all patients including children. I am conflicted about the idea of registration but feel that some sort of patient consent to indicate the knowledge of the potential risks be made but that the drug be made available. I also agree with the restriction in dose.

DR. HOLMBOE: Eric Holmboe. I agree with what has been said previously. I also feel that, if this drug is to be used in adults, there should be some sort of informed-consent process.

DR. GROSS: Peter Gross. A strong black-box warning, second-line drug and restricted to 12-and-a-half-milligram dose.

DR. WOOD: Alastair Wood. I would say the same thing, black-box warning. I would have a very restricted access

program in which consent would be obtained and, if it were to come back on the market, there would have to be such limited access that there would be an attestation and some clear ability of patients to consent. Similarly, in children, I think we should be careful not to just assume children are not at risk here. While I understand the sentiment to promote the drug in children, I think we need to be careful that we don't, then, put them at even greater risk with their lifelong hypertension risk, their lifelong exposure to cardiovascular risk factor, and so on when there might be safer drugs available.

DR. GIBOFSKY: Gibofsky. I would agree for restricting the dose to not above 12.5 milligrams in patients who need it for chronic use, not for acute use. I would favor a very strong black-box warning to emphasize the hypertension, cardiovascular, at the higher dose. I would favor language making this a less preferable agent, whether it is second or third choice, to be determined. I question whether this is something that might be handled, if it comes back, under a Subpart H where there would be very strong restrictions on who would have access to it based on need and determination of physician and patient.

DR. CRAWFORD: Crawford. In addition to what I stated with the other two, I think there should be a stronger black-box warning, dose limits as appropriate, duration limits, second-line and informed consent.

DR. CUSH: Cush. I would be in favor of retention of all current indications. However, I would strongly recommend removal of the 50-milligram dose from the market and its omission from the

package insert as a potential dose for use in acute pain. I would strongly encourage a black-box warning.

DR. BATHON: Bathon. I am strongly in favor of a strong black-box warning with elimination of the 50-milligram and this drug as a second choice. MS. MALONE: Malone. I have no problem with the black-box warning. I think, if it does come back on a market, that there have to be ongoing studies. And I am in favor of a patient consent that they acknowledge the risks that are involved. MR. LEVIN: Black-box warnings strengthened and I am intrigued by the notion of a Subpart H approach to limit prescribing and distribution of the drug.

DR. WOOD: That was Mr. Levin.

DR. ILOWITE: Ilo wite. A strong black-box warning, elimination of the 50-milligram dose. I would encourage reexamination of the dose in children in addition to the studies of blood pressure and atherogenesis that were talked about before.

DR. D'AGOSTINO: D'Agostino. Stronger black-box warning, dose restriction to 12-and-a-half and restricted access.

DR. MORRIS: Morris. Black box, withdrawal of the highest dose. I would like to see a consent, initially, but also, based on that consent, a reminder sent to the patient about either six months or a year, depending upon issues related to duration to remind them about the risks of long-term use.

DR. CANNON: Cannon. I favor a strong black-box warning, no direct-to-consumer advertising. I would limit its

use to a short-term use for pain in adults and for chronic use in children and young adults with JRA with careful monitoring of blood pressure. MS. SHAPIRO: Shapiro. I agree with what Dr. Cannon just said with some dose limitations, appropriate dose limitations.

DR. PAGANINI: Paganini. Black box to include very strong and severe dose and time restrictions as well as cardiovascular, to spell out the cardiovascular clearly to include blood pressure and congestive heart failure, no direct advertising and move from a patient brochure as a patient consent.

DR. FRIEDMAN: I agree with what has just been said with the elimination of the high 50 dose.

DR. HENNEKENS: Hennekens. I share Steve's concern that blood pressure is a greater potential issue here but Richard's that it is likely that higher doses of this drug lead to greater benefits. This may offer one plausible explanation for the higher risk seen in observational studies. As I said, with regard to the coxib, I think global risk assessment and aggressive management of cardiovascular risk is important. I would expand that I would definitely think we ought to be thinking about Ralph D'Agostino Framingham Risk Score and the aggressive management based on federal an AHA guidelines which are mandated based on these assessments for both statins and aspirin.

DR. SHAFER: Steve Shafer. If it is to be marketed, I think it should only be indicated for children not adequately treated with conventional NSAIDs. The black-box warning should state that the cardiovascular effects in children are

unknown and that the use in adults is not recommended. The adult use should be limited to compassionate use only

which, I believe, is the Subpart H restriction.

Voting Results for Questions 2B and 3B

DR. WOOD: Okay. I am now in a position to read you the votes for Question 2.b. and 3.b., at least for now. The vote for 2.b., which was the vote on

valdecoxib, for those of you who have forgotten already, was 17 yes, 2 abstain and 13 no. The vote on 3.b., which was the rofecoxib vote, was 15 no, 17 yes.

Slide with Text of Question 3

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 For Question 3C: Rofecoxib: Comments by Members

Surname	1st Name	Expertise*	Member Comments (in addition to previous comments for celecoxib and valdecoxib)
Abramson	Steven	Rheumatology	"stronger label in terms of hypertension and potential cardiovascular outcomes", "restriction of upper dose to be determined", "leave open the possibility of some change of this with future studies", "second choice" drug.
Nissen	Steven	Cardiology	Restrict dose to 12.5 mg "if anything is done with the drug),"I don't want to go there. But, if we do go there, I would put the most difficult and most complex warning on there possible".
Elashoff	Janet	Statistics	"Stronger than either of the two previous cases".
Gardner	Jacqueline	DSRMAC (Epidem.)	"Stronger", "register patients or otherwise bring attestation into the risk-management program", "good, strong postmarketing" evaluation.
Platt	Richard	DSRMAC (Epidem.)	"dose restriction".
Day	Ruth	DSRMAC (Psychol.)	"More restriction".
Furberg	Curt	Epidemiology	"Stronger black-box warnings".
Fleming	Thomas	Statistics	"same conditions and concerns that Steve Nissen indicated".
Domanski	Michael	NIH Research	"underscore second-line drug".
Boulware	Dennis	Rheumatology	Same as for celecoxib.
Dworkin	Robert	Anesthesiology	"third-line" drug , "a patient will have had to have failed two NSAIDs, whether selective or not, before they try this drug."
Hoffman	Gary	Rheumatology	"restriction in dose to 12.5 mg".
Manzi	Susan	Rheumatology	"restrict only the 50-milligram dose", "have patient consent" better than not having the drug available.
Farrar	John	Statistics	"strong black-box warning including an indication of ongoing monitoring of blood pressure in all patients including children", "I am conflicted about the idea of registration", "some sort of patient consent", "restriction in dose".
Holmboe	Eric	DSRMAC	"I agree with what has been said previously", if used in adults "there should be some sort of informed-consent process".
Gross	Peter	DSRMAC	"strong black-box warning", "second-line drug", "restricted to 12.5 mg dose".
Wood	Alastair	Pharmacology	"black-box warning , very restricted access program , attestation and some clear ability of patients to consent , "be careful not to put children at even greater risk with their lifelong hypertension risk, their lifelong exposure to cardiovascular risk factor".
Gibovsky	Alan	Rheumatology	restrict dose to 12.5 mg "for chronic use, not for acute use", "very strong black-box warning to emphasize the hypertension, cardiovascular, at the higher dose", "second or third choice", consider "Subpart H where there would be very strong restrictions on who would have access to it".
Crawford	Stephanie	DSRMAC (Pharmacy)	"stronger black-box warning", "dose limits as appropriate", "duration limits", "second-line", "informed consent".
Cush	John	Rheumatology	"removal of the 50-milligram dose from the market", "black-box warning".
Bathon	Joan	Rheumatology	"strong black-box warning", "elimination of the 50 mg" dose, "second choice".
Malone	Leona	Patient Representative	"ongoing studies", "patient consent"
Levin	Arthur	DSRMAC (Consumer)	"Black-box warnings", "I am intrigued by the notion of a Subpart H approach".
Ilowite	Norman	Rheumatology	"strong black-box warning", "elimination of the 50 mg dose", "reexamination of the dose in children", "studies of blood pressure and atherogenesis".
D'Agostino	Ralph	Statistics	"Stronger black-box warning", "dose restriction to 12.5" mg, "restricted access".
Morris	Louis	DSRMAC	"Black box", "withdrawal of the highest dose", patient "consent", "reminder sent to the patient about either six months or a year, depending upon issues related to duration to remind them about the risks of long-term use".
Cannon	Richard	NIH Research	"strong black-box warning", "no direct-to-consumer advertising", limit use "to a short-term use for pain in adults and for chronic use in children and young adults with JRA with careful monitoring of blood pressure".
Shapiro	Robyn	DSRMAC (Ethicist)	"I agree with what Dr. Cannon just said", "some dose limitations".
Paganini	Emil	Nephrologist	"Black box to include very strong and severe dose and time restrictions as well as cardiovascular", "spell out the cardiovascular clearly to include blood pressure and congestive heart failure", "no direct advertising", "move from a patient brochure as a patient consent".
Friedman	Lawrence	NIH Research	"elimination of the high 50" mg dose.
Hennekens	Charles	Epidemiology	"global risk assessment and aggressive management of cardiovascular risk".
Shafer	Steven	Anesthesiology	"If it is to be marketed, I think it should only be indicated for children not adequately treated with conventional NSAIDs", "The black-box warning should state that the cardiovascular effects in children are unknown and that the use in adults is not recommended", "The adult use should be limited to compassionate use only which, I believe, is the Subpart H restriction".