

# Questions from Committee to Dr. Verburg on Valdecoxib and Parecoxib

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

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### Highlights

- **RISK WITH DIFFERENT TYPES OF SURGERY:** Dr. Wood questioned the safety of valdecoxib in general surgery. Dr. Nessmeier (Pfizer consultant) said that valdecoxib should “be avoided in patients undergoing coronary revascularization” and by extension “any other revascularization” but that does not apply to other surgical procedures. Dr. Fleming expressed concern about a conclusion of safety in general surgery because of the low event rate in general surgery trials.
- **DATA INCONSISTENCIES:** Dr. Furberg was “troubled by some inconsistencies” in Pfizer’s briefing document. It was agreed that Pfizer would review Dr. Furberg’s concerns and would give a 10 minute presentation the following day on these issues.
- **RUPTURE OF UNSTABLE ATHEROSCLEROTIC PLAQUE:** Dr. Hoffman expressed concern that one mechanism for the increased cardiovascular risk in the CABG setting might be related to rupture of unstable atherosclerotic plaque; if this were the case, valdecoxib might be dangerous in non-surgical patients with unstable plaque. Dr. Verburg said “we are left with a lot of unknowns” and that Pfizer is “mindful of the concern that you raised”.
- **WOUND HEALING:** Dr. Hoffman asked about wound healing studies in animals. Dr. Seibert (Pfizer) said that valdecoxib did not affect incisional wound healing but Pfizer does not have data “in a vascular setting”.
- **RECOMMENDATION TO PROCEED CAUTIOUSLY:** Dr. Platt commented that the data are inconsistent and “the question is what is the cautious way to proceed while acquiring the additional information that we need to have? How important is it to think about the way these drugs are used while the additional information is being collected?”
- **VALDECOXIB PATIENTS NEEDING EMERGENCY VASCULAR SURGERY:** Dr. Friedman expressed concern that patients on valdecoxib might need emergency vascular surgery and asked if such patients would have to delay surgery for some time while valdecoxib was discontinued. Dr.

Verburg said he did not have an answer.

- **SPEED OF ONSET OF ADVERSE CARDIOVASCULAR EFFECT:** Dr. Nissen expressed concern that the CABG studies showed that “potent COX-2 inhibitors” can “produce events quickly even in patients taking aspirin” and over 10 days is a “pretty rapid emergence of the problem”.
- **POSSIBILITY THAT EFFECT MIGHT BE SHARED BY NON-SELECTIVE NSAIDS:** Dr. Abramson interpreted the CABG data as indicating that “if you inhibit COX-2 to a high degree you may get this result” and because aspirin was also on board, this might not be a selective COX-2 effect but might result from any of the non-selective drugs that also inhibit COX-2. Dr. Seibert (Pfizer) agreed with this comment and said “What we really don't know is the effect of an NSAID in the same CABG setting”. <Note: There is a double blind CABG study of naproxen vs. placebo that did not show a hazard of naproxen (Kulik et al, Eur J Cardiothorac Surg. 2004 Oct;26:694-700) to which TMT alerted Pfizer by email on 10/26/04.>
- **SELECTION OF PATIENTS FOR VALDECOXIB THERAPY:** Dr. Wood asked Dr. Seibert if she would take it if she “were at high risk of a platelet-driven problem”. Dr. Seibert referred the question to Dr. Strand, a Pfizer consultant, who said that he would not recommend valdecoxib for “a patient with high cardiovascular risk” but that valdecoxib is still needed as an “alternative for the patients who need chronic pain relief”. Dr. Wood asked if he meant that valdecoxib

should be used in “patients who have failed other therapy”. Dr. Strand said “I see it in patients who have high GI risk” and “in patients who have not already responded to celecoxib or may have been forced to discontinue Vioxx.”

- **MI DIAGNOSIS:** Dr. Furberg said that one should not use standard diagnostic criteria (particularly chest pain and enzyme changes) in diagnosing acute myocardial infarction in the post CABG setting. Dr. Nessmeier said that standard MI diagnostic criteria were not used (they used more rigid CK-MB and troponin criteria). Dr. Wood pointed out that the criteria were equally applied to the placebo and valdecoxib groups.
- **PROBLEM GIVING ANY DRUG WITH CV EFFECTS POST CABG:** Dr. Hennekens said that “any drug, regardless of its class, that would increase blood pressure, fluid retention and risk of heart failure, if given during or after CABG, would pose very difficult research and clinical challenges.”
- **THROMBOGENIC STIMULUS IN CABG TOO INTENSE TO BE REVERSED BY ASPIRIN:** Dr. Hennekens said “I would say to Dr. Shafer, regardless of the mechanism that is proposed, this is far beyond the powers of aspirin.”
- **NEED FOR THERAPEUTIC OPTIONS:** Dr. Shafer commented that the CABG setting is “an area where we do need improved therapeutic options and I would just encourage the committee to keep that in mind.”

## Discussion Text

DR. WOOD: I have a number of questions. In the general surgery study, there are a lot of issues about that that you didn't present. There is the same number of patients in that study as in the CAB study but many of these were women. They were much younger patients and the chance of seeing events in that study was extraordinarily small, don't you think?

DR. VERBURG: True. The underlying risk factors and risk factor status in the general surgery population was lower.

DR. WOOD: So, the general surgery study shouldn't give us any confidence to overrule the CAB study. Correct?

DR. VERBURG: I would not suggest that it would overrule the CB study. I would take note of the fact though that the cardiovascular events that occurred in the general surgery trial occurred at about an incidence of one percent. That was in the range of the incidence that we saw in the CABG surgery trial which ranged from 0.5 to 2 percent. So, although it doesn't completely put the issue to rest about to what degree the drug has a cardiovascular risk associated with it in the general surgery population relative to standard of care alone, the trial that we have conducted, we believe, moves us down that road considerably.

DR. WOOD: What percentage of the general surgery patients were women?

DR. VERBURG: I believe that was 60 or 70 percent female.

DR. WOOD: And they were getting minor gynecological surgery largely?

DR. VERBURG: Actually, the largest percentage of surgeries was gastrointestinal, followed by orthopedic and then gynecological.

DR. WOOD: And do you recall the age difference between the two groups?

DR. VERBURG: No. I can find that.

DR. WOOD: I think it is about 10. I think it is more than 10 years. The other issue that we are here to address is the total safety of these drugs. I wonder if you can show us Table 3 from your paper in The New England Journal, or perhaps you can go through it? It is the one that shows the incidence and risk ratio of your predefined adverse events in the CABG study.

DR. VERBURG: I don't have that on a slide.

DR. WOOD: You are the author on that though, right?

DR. VERBURG: That is correct but I don't have a slide.

DR. WOOD: Well, let me help you. Every one of the predefined adverse events has a relative risk of greater than 1, and not all of them significant but every one of them greater than 1. So, I was sort of intrigued by the slide that said there was obvious benefit of this

drug in surgical patients. Tell me how I would recognize the benefit given these predefined adverse events.

DR. VERBURG: I would like Dr. Nessmeier to come up and make some comments. Dr. Nessmeier was also an author of the CABG surgery paper, and a practicing anesthesiologist.

DR. NESSMEIER: I would just like to say that the selective COX-2 inhibitors I think are potentially an important tool in the armamentarium from the standpoint of an anesthesiologist for treatment of postoperative pain, given that the alternatives also have side effects. Right now we have, obviously, the opioids and the narcotics cause dose-dependent respiratory depression and cause, you know, excessive sedation that is also dose-dependent, as well as nausea and vomiting, ileus, urinary retention. One has to wonder if morphine, for instance, would be approved if it were subjected to intense scrutiny today. In addition, we have the non-selective non-steroidal anti-inflammatory drugs as potential therapy for postoperative pain, but they also are not without side effects. The one that is most commonly used by anesthesiologists in the perioperative setting would be ketololac and that has, as you know, the potential that surgeons worry about for post-surgical bleeding problems, the potential for gastric ulceration and also renal dysfunction. So, given that the alternatives also have side effects, it is I think reasonable to continue the study of this drug, and it has been approved in over 40 countries. I know my colleagues elsewhere are very favorably impressed with its analgesic potential, you know, primarily in relatively low risk patients. Certainly we have demonstrated that it should be

avoided in patients undergoing coronary re-vascularization. I would certainly extend that, just based on common sense, to any other revascularization procedures. But that does not apply to the majority of general surgical procedures, gynecologic surgical procedures, orthopedic surgical procedures. We have no evidence that any of these concerns apply right now to the lower risk patients who are undergoing the vast majority of surgical procedures worldwide.

DR. WOOD: But, Nancy, if you look at your table, greater than one confirmed adverse event, that includes everything you have predefined and that is presumably what we are looking for, and the relative risk was 1.9, with a p value of less than 0.01. And, the events were not all cardiovascular--renal failure, upper GI events, every one of them--surgical wound events, every one of them, death even, has a relative risk of more than 1. So, I agree there may be an advantage but, in the absence of demonstrating that advantage and in the presence of clear risk, I don't see where the advantage is here.

DR. NESSMEIER: Well, the risk is well demonstrated now in coronary-artery bypass grafting population. It just hasn't been seen in any of the other studies, including the large general surgical study that was just completed and that we are in the process of writing up. That was over 1000 patients. But there are these 19 other smaller studies and it hasn't been seen in any of them in the other populations. I certainly agree that further study is needed because it is a vast population we are talking about, and the power to demonstrate absolute safety is also vast.

DR. WOOD: Tom?

DR. FLEMING: I have a very parallel set of observations. I thought the final conclusion on B-36 was very strongly worded, unique benefits over existing analgesic medications and a favorable benefit to risk when, in essence, the general surgery study has ten events and you have four times that many events in the two CABG trials. And, you were referring to The New England Journal article. We can also go to the background material at Tab Q, page 18, and we see a very similar, striking global safety profile when you look at the SAEs in the 035 trial. There is a doubling in SAEs from 10 percent to 20 percent. When you look overall at GI SAEs, it is 0 against 7; cardiovascular renal SAEs, 7 against 33; cerebrovascular events, 9 against 1; thrombophlebitis, 3 against 0; atrial fibrillation, 2 to 1; MIs, 5 to 1. Now, the events that we saw, 15 to 2 just had 1 to 1, but I think the reported before adjudication events were 2 against 9. Then, pulmonary postoperative, 5 against 37. So, a very striking increase across a wide array of different SAE categories in the CABG setting for both of the trials.

DR. WOOD: Curt?

DR. FURBERG: Well, I am troubled by something else. I am troubled by some inconsistencies that I have found in the briefing document from Pfizer. I would like to just briefly go over some of them. On page 55 there is a summary from acute pain studies. It says here are the safety data from 18 clinical studies. On page 76 in the summary it says here are the safety data from 20 completed studies. I just wonder what happened to

the other two trials. They disappeared. Any suppression of information or is it just an error?

DR. VERBURG: We will check on that.

DR. FURBERG: The other thing relates to the overall findings from these summary studies, the 18 studies. In Table 19, on page 60 for acute myocardial infarction it says placebo, 0; valdecoxib, 3. In the following table for myocardial infarction it says 1 versus 3. So, there is an internal inconsistency in two tables after each other. What is even more striking is that when you start looking at the individual studies that contributed to the summary statistics for the 18 studies--I just looked at two of them, the study we just talked about, the general surgery study. In terms of myocardial infarction, depending a bit on how you define it, there were 3 and 2. If you include cardiac arrest and sudden cardiac death it is 6 to 0. The summary statistic was 0 to 3 or 1 to 3 and here I have 6 in one study. I add in the data from one of the bypass surgery trials and I get additional numbers. So, just by combining the bypass surgery trial 071 and the general surgery for MI I have 0 to 8 or 1 to 9; not 1 to 3. And how about the other 16 studies? That is troubling. I also find that they included in the summary statistic one of the bypass surgery trials but not the other one. Why? I mean, the other study met the same definition. If you put that in the numbers get even worse. So, there is clearly an under-reporting of events the way I interpret it, and I have to say that we all make mistakes, and most of them are honest. Honest means that sometimes you benefit from your mistakes and sometimes you are hurt. But here all the inconsistencies tend to go in one

direction. So, I just raise the question whether these are honest mistakes. It has made me wonder how much trust I can have in the information that we have received.

DR. WOOD: Dr. Hoffman?

MR. HARRIGAN: Excuse me--

DR. WOOD: All right.

MR. HARRIGAN: This is Ed Harrigan from regulatory affairs at Pfizer. We would like to have ten minutes. We are not prepared at this point to go through table by table to look at the questions that you have. We would like ten minutes tomorrow to do that and I think we will quite readily answer all the questions you raised.

DR. WOOD: Okay, that is helpful. Dr. Hoffman?

DR. HOFFMAN: I would like to just raise some questions that are extrapolations from the CABG study where your explanation for why there may have been increased events is both provocative, interesting and perhaps, in fact, true. But what if this is a phenomenon that does not have to do with just perturbation of endothelium and cross-clamping, etc.? What if the patients going through a CABG in fact are going to CABG because the lesion that they have represents a generalized high plaque burden, unstable plaque? We would all agree then that, if we were to extrapolate from that, we would not give perhaps any drugs in this class to people at considerable cardiovascular risk that we knew of. But the problem in chronic therapy for patients with RA and OA is that many of them come to us

with perhaps moderate to even severe coronary-artery disease that is clinically silent. Even with extensive screening we may not be able to pick up those patients. We can only postulate that those patients will be the tip of the iceberg that may have events because of the physiologic effects of COX-2 inhibitors and perhaps Bextra in particular because of what the data is that you have reviewed with us. So, I am concerned that you would advocate, given these unknowns, the use of Bextra still in patients who have OA and RA and might be taking that drug for years, given that we don't have data that goes significantly beyond six months to a year long term.

DR. VERBURG: Would you like me to respond? Our position is that, again, we are shaped really by a lack of understanding about how other agents would act in the CABG surgery setting. I think your point is a good one. You do not know whether patients are entering CABG and the result is because of their history, the procedure or some combination of the whole. So, we are left with a lot of unknowns and we are left with trying to shape conclusions based on the data we have in the arthritis populations, being mindful of the concern that you raised.

DR. HOFFMAN: A follow-up to that but not directly related to that is, while you have shown good efficacy for analgesia postoperatively and have provided a caution about why you would not use Bextra postoperatively for not just cardiovascular disease but vascular surgery in general, do you have any data from animal models that tells us anything about wound healing after

vascular surgery in animals given Bextra and not given Bextra?

DR. VERBURG: Not that I have information specifically about wound healing following vascular surgery, we have done wound healing experiments with Bextra and the other agents. If you would like a quick synopsis of those, we can do that. Dr. Seibert or Dr. Kahn, can you make some comments in that respect?

DR. SEIBERT: Dr. Seibert, pharmacologist for Pfizer. We have looked directly at wound healing, looking at incisional wound repair, tensile strength and seen no effect at super-therapeutic doses of compounds like valdecoxib, celecoxib. If wounds are infected there may be some delay in that wound healing process. We are aware of that. We have no direct evidence that there is a direct effect on wound healing in an incisional setting. We have no direct experiments looking in a vascular setting at this point.

DR. PLATT: It seems to me that in addition to having to make decisions without having all the information we would like, we have to make decisions around data that are internally not consistent with one another. That is, a lot of different studies come from a lot of different place and say things that can't all be fit into a single coherent framework. For instance, I take your point that the observational studies of Bextra seemed to show no real increase compared to other non-steroidals. On the other hand, there are observational studies of other non-steroidals that seem to show that they don't have increased risk compared to no drug and, yet, there is a good placebo-controlled study of

valdecoxib that shows quite a lot of risk. So, I don't know a way to them all together. It seems to me--this is a statement to my colleagues on the committee, we have a tough job of saying not only is there a lot we don't know but we are going to have to decide which pieces of the information we do have to put the most weight on. Just to sort of herald the discussion that I know we will have, the question is what is the cautious way to proceed while acquiring the additional information that we need to have? How important is it to think about the way these drugs are used while the additional information is being collected?

DR. WOOD: Agreed. Dr. Paganini? No? Was there somebody else down there? Go ahead.

DR. FRIEDMAN: Sometimes vascular surgery, cardiovascular surgery in particular, has to be conducted on an emergency basis. How do you deal the case of people who may have been on Bextra, for example, and then need surgery? Do they have to be off for a period of time, or what policy are you advocating?

DR. VERBURG: Bextra is not approved for acute pain so if we are talking about placing a patient perioperatively on Bextra--

DR. FRIEDMAN: No, no, I am talking about people who may have been on it for arthritis but then need emergency surgery.

DR. VERBURG: Well, I don't know that I have any specific recommendations on that. I haven't really envisioned that. I do know that patients undergo surgical

procedures with selective COX-2 inhibitors routinely without discontinuing medication due to the fact that they do not result in excess bleeding. But I don't know that anybody has really thought through the implications of the scenario that you just brought up.

DR. WOOD: Dr. Nissen?

DR. NISSEN: I am going to suggest a conclusion from this study and I want to see if you agree with it, that what we learned from the CABG study is that a sufficiently high dose of a potent COX-2 inhibitor, given for only ten days to a group of people also taking aspirin, is capable of producing a highly significant increase in cardiovascular thrombotic events. What is unique about this study from my perspective is the rapidity with which the events occur with relatively short-term exposure. So, doesn't it tell us that the potential exists for potent COX-2 inhibitors to produce events quickly even in patients taking aspirin? I mean, I think that is something we haven't talked about with this study. Everybody got aspirin, as I understand it. So, this is a pretty rapid emergence of the problem. We heard about an 18-month delay in another study and everybody was talking about, well, is there an inflection point and so on? This is only ten days of therapy. So, isn't that the proper conclusion from the study?

DR. VERBURG: I would tend to agree. The onset was obvious by the time to event curves. All those rapid events tended to be stroke events in both trials, which is also somewhat puzzling and a little bit different from the types of events that we have been seeing in other settings.

DR. WOOD: Any other questions?

DR. FLEMING: Just one thing to add to what Steve is saying, and that is just the absolute increase. We have seen that in terms of a relative risk increase this is a multi-fold increase but these are frequently occurring events. So, in the 035 trial when we are looking at the denominator of 311 people we are talking about cerebrovascular accidents in 9, an overall event rate increase from 1.3 to almost 5 percent. So, it is a tripling in the overall rate but to an absolute occurrence of 1/30 persons treated.

DR. NISSEN: You are suggesting sort of the number needed to treat in order to get an event is relatively small.

DR. WOOD: Steve?

DR. ABRAMSON: I think it also speaks to the fact that, because aspirin was present, perhaps the importance of COX-2 in this acute event of cardiovascular insult but because aspirin was present it simply says if you inhibit COX-2 to a high degree you may get this result. It doesn't say that it is a highly selective COX-2 agent that is necessarily responsible. It may simply be the process of inhibiting COX-2. So, I think we have to separate whether this is a selective COX-2 effect. The presence of aspirin basically says it is not a selective COX-2 effect; it is the importance of COX-2 derived prostaglandins in this setting that one is aborting.

DR. SEIBERT: I could just add--I know it is late in the day but, you know, I think that is exactly one of the points we want to raise, that the setting that we see these

results in, in CABG, seems quite different, as Dr. Nissen pointed out, from what it takes in very chronic exposure in the arthritic patient. In fact, that evokes quite possibly very different mechanisms or very, very different places in the continuum. What we really don't know is the effect of an NSAID in the same CABG setting because we haven't seen direct comparator studies performed, and we would not be interested in doing them at this point. We have conclusive evidence. But this is quite different than the mechanism that we try to unify around the NSAIDs and the coxibs like celecoxib in the chronic setting, where we believe hypertension is the driver there. And, if rofecoxib stands outside of that with unique properties then perhaps it does. So, we are really believing that we are working with very different hypotheses and mechanisms here.

DR. WOOD: Well, would you take it if you were at high risk of a platelet-driven problem?

DR. SEIBERT: I am sorry, I don't know where the question came from.

DR. WOOD: Here. I mean, given that CABG is a model of platelet-derived problems, would you take a drug if you had some other problem that looked like that?

DR. SEIBERT: Well, I would get right to the issue of risk/benefit and what your alternatives are.

DR. WOOD: And the benefits from Bextra in clinical trials like VIGOR or what?

DR. SEIBERT: I guess we would have to get right to the issue of risk/benefit here and, you know, perhaps that is best addressed in terms of that risk/benefit in that setting by our clinical consultant.

DR. STRAND: May I answer you--

DR. WOOD: Sure.

DR. STRAND: As a practicing rheumatologist, and I teach at Stanford. Bibica Strand. I think all of our patients do not respond uniformly to one non-steroidal. Similarly, they don't respond to COX-2 uniformly. Thus, we need multiple agents, and we have a group of patients with chronic OA, rheumatoid arthritis, even motor vehicle accidents who need anti-inflammatories on a regular basis. Would I recommend that a patient with high cardiovascular risk be taking one of these agents at the present time based on the data we just discussed, the answer would be no. But I think that there is a risk/benefit profile here that is positive in terms of understanding that these patients need treatment for their chronic pain. In fact, there is a GI benefit and, in fact, except in this setting which may be confounded somewhat from aspirin in terms of the CABG studies, we don't yet see an increased risk with Bextra. It does not have an increased risk for hypertension or edema until you get to 40 or above, and the doses are 10 in clinical use. I think the other point to be remembered is that in this CABG study, and of course it is confounded and one cannot say that there is absence of evidence and presence of safety, but many of those cardiovascular events also occurred either on placebo or more than five half-lives after the drug was stopped in the period of time of follow-up when we are not clear whether aspirin was

continued or not. So, I think it is very difficult to understand what happened with many of the delayed events. If we look simply at the valdecoxib and placebo arm versus placebo, we don't see the same signal. So, from that point of view I would argue that we still need this alternative for the patients who need chronic pain relief.

DR. WOOD: Well, we are lurching towards conclusions here perhaps by Friday. What you are saying is that the patients you would see it in are patients who have failed other therapy?

DR. STRAND: I see it in patients who have high GI risk but, in fact, most of our OA and RA patients already have increased risk and many of them have already had GI bleeds because they have tried chronic non-steroidals for a long period of time. I see it in patients who have not already responded to celecoxib or may have been forced to discontinue Vioxx.

DR. WOOD: Let's move on to the next speaker and, hopefully, that will be our last for tonight, you will be sorry to hear.

DR. FURBERG (Bextra Comment added at beginning of Discussion of naproxen presentations): A couple of comments, one regarding Bextra. I applaud the FDA in the effort to standardize myocardial infarction, but to apply the standard criteria of myocardial infarction to patients undergoing bypass surgery doesn't make any sense because you are opening the chest so the whole criterion about pain doesn't make sense. The other one is that many of them have increases in their enzymes. You cannot apply the regular criteria to myocardial

infarction to the population. So, I just think that reclassification is not valid.

DR. WOOD: Nancy?

DR. NESSMEIER: Well, just a comment about the CABG study, the criteria were different in that it was diagnosed either by autopsy or by CK-MB level of more than 25 ng/mL within the first 72 hours after CABG, or an excess of 10 ng/mL if more than 72 hours had gone by, or a peak troponin of more than 3.7 mcg. So, those are more rigid criteria than would be used for a non-surgical study.

DR. WOOD: Right, and there was a control group so it should have shaken out. Right?

DR. NESSMEIER: Correct.

DR. HENNEKENS: (Bextra Comment added at beginning of Discussion of naproxen presentations): First of all a comment about the CABG surgery data, in terms of benefit to risk assessment, I would believe that a priori any drug, regardless of its class, that would increase blood pressure, fluid retention and risk of heart failure, if given during or after CABG, would pose very difficult research and clinical challenges. I would say to Dr. Shafer, regardless of the mechanism that is proposed, this is far beyond the powers of aspirin.

DR. SHAFER: I just want to re-echo what Dr. Nessmeier said. The CABG population is very different, very much a pro-inflammatory population. In anesthesia we do very poorly at treating postoperative pain, particularly in the first 24, 48. Multimodal therapy is what we are looking for and certainly if you

say the CABG population is very different and you look at the data in the acute surgical setting--brief administration--it is an area where we do need improved therapeutic options and I would just encourage the committee to keep that in mind.