

Committee Questions to the Naproxen Speakers

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

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Highlights

- **EVENT CLASSIFICATION:** Dr. Furberg was concerned about lack of prespecified event definitions and lack of event adjudication in the ADAPT trial.
- **INTERPRETATION OF DIFFERENT CV HAZARD RATIOS OF NAPROXEN AND ROFECOXIB:** Dr. Hennekens asked if the results in VIGOR were because naproxen was beneficial, because rofecoxib was harmful, or a combination of the two. Dr. Huber said “I don’t know”.
- **INTERPRETION OF OBSERVATIONAL STUDIES:** Dr. Fleming said it was difficult to rule out a doubling of a common event such as MI from the naproxen exposure data. Dr. Huber responded that for the observational studies “there is some weight to that evidence. It shouldn't be completely put aside.” Dr. Fleming replied that observational studies make it difficult to detect an increase in a common event “unless you are looking for a ten-fold increase”.
- **INTERPRETATION OF LONG TERM CONTROLLED DATA:** Dr. Fleming focused on the long term controlled studies and there are only three. Two (VIGOR and TARGET have a coxib comparison) and the third (ADAPT) has a placebo control group for which there was a suggestion that the data monitoring committee stopped the trial due to and increase with naproxen in “GI bleeds, cardiovascular and cerebrovascular events”. Dr. Huber said that in “the NIH press release there were approximately 70 cases, and what was stated about it was that there was--I can't remember the exact wording of the text, but it was an increased risk of stroke or MI.” Dr. D’Agostino said that the comments that Dr. Fleming was making “are very important.”
- **RISK BY DURATION OF NAPROXEN THERAPY:** Dr. Morris asked about the effect of duration of therapy. Dr. Thacker (Roche epidemiologist) responded that “None of the studies really gave us any data on duration of use.”
- **ADAPT TRIAL NAPROXEN DOSE WAS THE OTC DOSE:** Dr. Witter said that “in the ADAPT trial naproxen was the OTC dose.”

Discussion Text

DR. WOOD: Great, and thanks for going through that so quickly. Kimberly tells me that the committee on breast implants went to eleven o'clock so we have a bit to go yet before we beat them. Anyway, we will take questions for the last group of speakers. Curt?

DR. FURBERG: A couple of comments <see Bextra discussion for first point and Dr. Nessmeier response> The second point is related to the ADAPT. you can add to your list of limitations of the study that there is no prespecified outcome for cardiovascular events. The investigators looked at a number of them and it is not clear which one they decided to put their money on. And, there is no adjudication of the cardiovascular events. They were all self-reported--very, very soft data.

DR. WOOD: Yes, Dr. Hennekens?

DR. HENNEKENS: I have two comments and a question. <see Bextra discussion for first comment> The second comment to Dr. Huber as regards his reassurances from the observational comparisons, I am concerned that for small to moderate effect there are biases confounding by indication, and uncontrollable confounding inherent in all case control cohort studies, no matter how large or how well designed, as well as their meta-analysis. They can either produce false evidence of benefit or harm or false evidence about lack of benefit or harm. I just think the randomized data are far more important, which leads me to my question to Dr.

Huber. In VIGOR, do you believe the overall randomized findings are attributable to a hazard of rofecoxib, benefit of naproxen or some combination of the two?

DR. HUBER: I don't know.

DR. WOOD: That is a surprise! Other questions? Dr. Shafer?

DR. SHAFER: <See Bextra discussion>

DR. WOOD: Other comments? Yes, Tom?

DR. FLEMING: Just looking at the nature of the data that we have been provided here, slide 10 where we looked at naproxen exposure data with millions of doses and the sponsor basically said there is no safety signal for cardiovascular events or MIs. I guess if we were looking at rare events, Stevens-Johnson's rash or something like this, this kind of evidence could be reassuring. But how is reassuring when we are looking at MIs and strokes where you expect to see a certain rate of these in natural history? How do we rule out a doubling? So, essentially it leads me to really wanting to focus on the randomized trials as having a sense. Looking at slide 17, I am worried about how little of this information is longer term exposure. So, if I am understanding correctly, we really have TARGET and VIGOR and ADAPT as maybe the best bases for making an assessment over a longer term in a truly controlled fashion for effects on cardiovascular-related

major events--cardiovascular death, strokes and MIs. Two of those, VIGOR and TARGET, we don't have a placebo control. The questions that were just raised I think by Charlie Hennekens are in VIGOR--basically how do you make an assessment there without a placebo control? ADAPT is a placebo control. We heard just now that the data monitoring committee specifically didn't stop the trial on 12/10/04. By my notes earlier this morning, I thought we were told that the data monitoring committee on that date did stop the trial due to naproxen GI bleeds, cardiovascular and cerebrovascular events. So, I am a little confused about what actually did happen. Is it true at this point though that we don't have first-hand access to what the data actually are in ADAPT?

DR. HUBER: Let me answer your first comment about the randomized clinical trials. Basically what you said was that the TARGET and the VIGOR studies are the large randomized, comparative trials. There is also the Alzheimer's study which is obviously much smaller but it is one-year follow-up. With regard to the postmarketing data, we recognize the limitations. We were just wanting to reassure you that there hadn't been numerous case reports out there. Also, when we look at disproportionality there is really no signal there. It is something we use in postmarketing surveillance. I would be careful on the observational studies. Recognizing the limitations as stated, that does give us a large number of patients who have been exposed to naproxen and gives us some, we believe, important data. There are 80,000 exposures in that series of observational studies. So, we do believe there is some weight to that evidence. It shouldn't be completely put aside.

DR. FLEMING: And the weight you are placing on that is you are reassured about what specific outcomes?

DR. HUBER: That for MI, for myocardial infarction with 11 observational studies, we see a consistency of finding that is at 1 or lower.

DR. FLEMING: But doesn't the fact that we have 11 of those give us a more precisely biased estimate? How do you know that all 11 aren't in fact subject to the same type of systematic bias and under-detection?

DR. HUBER: Well, we use multiple databases. There are different comparisons. There are past users in several of the studies. I guess the question is if we take that approach, then we have to question should we even do observational studies for any issue?

DR. FLEMING: Not necessarily. It depends on what you are looking for. My comment was if you are looking for MIs and strokes, which are events that would in fact occur in natural history, unless you are looking for a ten-fold increase, isn't it really difficult for that type of outcome to truly be able to rule out a relative risk of 1.5? I would argue, yes, it is. While there are other things that were reassuring, if we wanted to be reassured about stroke and MI, this is where it is intrinsically the most difficult.

DR. HUBER: I agree you. I don't think we should rule things out on the basis of the observational data, but I think what is important is when we looked at this a priori based on mechanism of action,

etc., the data was telling us there was probably not an increased risk. So, when we take that as the first line of evidence and then we put on the additional lines of evidence, at this point in time the only data suggestive of an increased risk, to our knowledge, is the release of the preliminary findings of ADAPT.

DR. FLEMING: Can you clarify that? Because I believe we heard something different this morning about what actually has been stated. Can you clarify what actually has been stated?

DR. HUBER: What we are talking about is the NIH press release. I believe there were approximately 70 cases, and what was stated about it was that there was--I can't remember the exact wording of the text, but it was an increased risk of stroke or MI.

DR. WOOD: Well, we are going to hear about that on Friday morning.

DR. FLEMING: So, we will hear about it on Friday?

DR. WOOD: Yes, unless we keep talking until then, I guess. It is down for 8:10 on Friday morning. Other questions? Yes?

DR. MORRIS: Dr. Huber, while you are there, did any of the observational studies stratify by time on drug? And, was there any different finding by length of time on Naprosyn?

DR. HUBER: I am going to have to look to my epidemiologists? Dr. Thacker is the epidemiologist for Roche.

DR. THACKER: We did an extensive literature review of all the studies that

were published up to December, 2004. None of the studies really gave us any data on duration of use.

DR. WOOD: Other questions? Yes?

DR. WITTER: I just want to make the point that in the ADAPT trial naproxen was the OTC dose.

DR. WOOD: Any other questions or are we finally getting exhausted? Yes, Ralph?

DR. D'AGOSTINO: Just because we are exhausted, that doesn't mean that what was presented is, in fact, something we can buy. I think the comments that Tom is making are very important. We have all this meta-analysis. We don't know anything about those studies. So, I think we have to wait until we hear from the NIH.