

Summary of Meeting Presentations (FDA): Sharon Hertz MD

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

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Highlights

- **SOME COX-2s NOT APPROVED BY FDA:** FDA has not approved all COX-2 NDAs, in some cases because of cardiovascular concerns.
- **INCREASED RISK BUT RESULTS NOT CONSISTENT:** This meeting has identified “increased risk for cardiovascular events” but results “are not consistent across studies and across situations”.
- **MULTIPLE MECHANISMS POSSIBLE:** “It is possible there is more than one mechanism”.
- **TIME TO ONSET OF RISK IMPORTANT:** Another important issue is “time to onset of risk”.
- **DECISIONS REQUIRED DESPITE UNCERTAINTIES:** Despite all the uncertainties, “we have to move forward” and decide the role of currently approved products, and what new studies to do.
- **COMMITTEE QUESTIONS:** For Questions 1-3 (celecoxib, valdecoxib, rofecoxib) – CV risk, support for marketing, appropriate populations, risk-management) the answers will depend on whether there is considered to be a “fairly uniform” class effect. Question 4 asks if aspirin mitigates a cardiovascular risk of COX-2 drugs. Other questions address the “potential G.I. benefits for these same products”, labeling and risk-management recommendations (and the extent to which these should be “class”-based), additional trials for non-selective NSAIDs, and approval requirements for new drugs.

Presentation Text

DR. HERTZ: There are now several versions of my slides around and you are

free to look at whichever interests you. There is one correction on the

lumiracoxib slides from the original set where I substituted the word diclofenac for ibuprofen. So those of you looking at those slides just be aware of that, please.

What I am really just going to do now is just focus down again some of the reasons why we are here. This would not be the current slide set. Any help here?

Looking at the most recent set that were handed out, and we will just work from there because there is not a lot of data anymore to present, but, basically, I want to just point out that we are here because we do recognize that pain drugs are critically important, that the COX-2-selective NSAIDs have been extensively studied and there are, over time, studies that revealed new potential uses as well as new risks.

We need to determine how we feel about these risks. Are they limited to individual products? Are they applicable across the group of COX-2 selectives and how far does this extend to the nonselective anti-inflammatories.

There is a slide that describes—

DR. WOOD: Sharon, apparently everybody has hard copies of your slides.

DR. HERTZ: Right.

DR. WOOD: So if you want to just go through them and refer to the slide number, that would probably be helpful to people.

DR. HERTZ: Okay. If we go to the third slide, you can get a sense of the sizes of the databases that were presented in the

individual reviewer descriptions of FDA reviews.

A couple of points. The numbers there reflect predominantly patients on the drug of interest as opposed to the entire database. The outcome studies are more reflective of the entire populations including comparators. These drugs were assessed and have been assessed over time in fairly large numbers of patients.

I think it is useful to note that we have not approved, in this country, all of the COX-2-selective NSAIDs that have come to us in applications for a variety of reasons. Some of these may be related to cardiovascular-risk assessment. Some may be related to non-cardiovascular-risk assessment which we really haven't gotten into in this setting.

In addition, you may also note that parecoxib has not yet been approved in this country although it has been approved elsewhere. So I think that we have a lot of issues to consider with these products.

When we reviewed the studies that have been presented, we see that there is some increased risk for cardiovascular events but one of the key issues here is that the results are not consistent across studies and across situations. We also have seen that there is risk that is being associated with some of the nonselective products.

So we have a story of conflicting data. I am up the Slide 5. We have data that has been present across short- and long-term studies, the epidemiologic studies. The challenge is to compare across populations, across comparators. It is

striking that sometimes very similar study designs have very different results.

It is possible there is more than one mechanism. Again, the data has been inconsistent with the NSAIDs. We also have conflicting information coming back on what occurs in the context of concurrent aspirin use. It is really unclear if aspirin use has a truly meaningful effect on whether there is any G.I. benefit of the COX-2-selective products. That has not been clear either.

I have been asked to point out that, in addition, time to onset of risk is something that we need to consider very importantly, too, which, again, is something that is evident when we look at the study data and important in our deliberations for this.

So, in spite of this conflicting data and the many questions, we have to move forward. We have to determine what the role of approved products are on the market today, what additional studies are necessary, what studies would be most helpful.

I am going to summarize and combine some of the questions that we have posed. These are questions we dearly would like input from the committee. To start, if we think about the first three questions, does 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 U.S. If yes, in whom? And which of the potential benefits of celecoxib or the others outweigh the potential risks and what actions would

you recommend that we consider implementing to ensure safe use?

I think it is also important to understand that some of these answers are going to depend on if we think that this is a fairly uniform class effect and, if not, we are going to have weigh the amount of information available for each of the products. It is not the same. We don't have the longer outcome studies, for instance, with valdecoxib at this point.

Question 4 asks if the available data support a conclusion that one or more of the COX-2-selective agents increase the risk of cardiovascular events and what is the role of concomitant aspirin in attempting to mitigate that risk. What additional clinical trials or observational studies, if any, would you recommend as essential for us to further evaluate celecoxib, rofecoxib and valdecoxib?

What about to further evaluate the potential G.I. benefits for these same products? Would you recommend that the labeling for these products include information regarding the absence of long-term controlled clinical-trial data assessing potential cardiovascular effects and if you have a recommendation for how that should be conveyed in terms of warnings, boxes and such.

What additional trials would be essential to evaluate the nonselective nonsteroidal anti-inflammatory drugs particularly with respect to cardiovascular risk? Similarly, what will now become essential for products under development prior to approval to help gain approval?

We have to determine what studies would be necessary to evaluate the cardiovascular risk of these products and

how much information do we need to know about the gastrointestinal risk? If pre-approval studies recommended as essential do not demonstrate an increased risk for a cardiovascular event, how would you propose the FDA handle that information in the labeling? Would the absence of a cardiovascular-risk signal preclude the need for any warnings or precautions in the labeling of a new product or should we rely more on a class warning or precaution in the absence of a signal of increased risk in the pre-approval databases?

If you think a class warning is appropriate, please advise with particular attention to whether you recommend it apply to all NSAIDs or only COX-2-selective NSAIDs.

So I want to thank everybody here for their time and their commitment to helping us through this extremely challenging program and we really look forward to hearing your deliberations and your recommendations. Thank you.