

# Sponsor Two-Minute Statements

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

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

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## Highlights

- **PFIZER:** Celebrex has received more extensive safety evaluation than non-specific NSAIDs, and is effective in arthritis and familial adenomatous polyposis. The daily dose of Celebrex is 200 mg/day or less in three-quarters of patients. Celebrex has a favorable GI profile. Celebrex has not shown an increased cardiovascular risk in arthritis patients. In three long-term placebo controlled trials, increased cardiovascular risk was noted only in the APC study. The final results of the ADAPT trial will clarify the relative cardiovascular safety of Celebrex and naproxen.
- **MERCK:** New data show that increased cardiovascular risk is not unique to Vioxx and appears to be a class effect. The large MEDAL study will compare the relative risks of COX-2 inhibitors and traditional NSAIDs.
- **NOVARTIS:** Cardiovascular risk, GI risk, heart failure, cardiorenal profiles, and blood pressure effects are not well correlated with the degree of COX-2 selectivity. Lumiracoxib was associated with significantly less blood pressure effect and a 79% reduction in GI complications in the TARGET study. Duration of use should be restricted to that supported by the data. There should be a robust risk-management program, including firm post-marketing commitments.
- **BAYER:** Bayer's Aleve brand of naproxen is a safe and effective pain reliever suitable for OTC use. Bayer appreciates the comments by the committee that the public reports on the ADAPT trial may have caused significant physician and consumer confusion.

## Presentation Text

DR. WOOD: Thank you very much. The companies have also asked for two minutes to respond. We all heard the rules yesterday so it is: Two minutes. Microphone gets turned off two minutes later and lips just keep moving.

### **Pfizer**

DR. HARRIGAN: Could I have Slide No. 1. This is Harrigan from Pfizer. What I would like to do is first to summarize what we know about celecoxib and what we think that tells us about the benefit:risk equation for that drug.

I make the point in this slide about Celebrex being extensively studied and to remind the committee of the contrast of the very widely used nonspecific NSAIDs.

On the next point, we see that efficacy has been demonstrated in arthritis pain and familial adenomatous polyposis.

Our prescription data and observational study data tell us that approximately three-quarters of patients who are taking celecoxib are receiving daily doses of 200 milligrams or less.

Celebrex does have a favorable G.I. safety profile, a point emphasized by the very relevant G.I. safety findings that we heard about this morning from ADAPT compared to over-the-counter doses of naproxen.

Cardiovascular risk was not detected in the setting of treating arthritis patients understanding all the caveats about that data that we have heard over the past two days. In APC, an increase in cardiovascular risk was reported apparently in a dose-related pattern. In contrast, two additional long-term placebo-controlled trials did not find evidence of increased cardiovascular risk at daily doses of 400 milligrams.

The comment about the ADAPT findings is supported by the initial announcements from National Institute of Aging. We await that data with great interest, particularly given the size, the duration in the elderly population study which would lead us to believe, expect, that the number of events in that trial will exceed the number of events in either or both of the other two trials combined.

The final ADAPT data and the polyp efficacy data will make significant contributions to our understanding of the benefit:risk. In addition, as (microphone turned off.)

DR. WOOD: Next speaker? It might be worthwhile introducing yourself just so we know which company you are representing.

## **Merck**

DR. ERB: Dennis Erb, Regulatory Affairs at Merck. On behalf of Merck, I want to again thank the committee and the FDA for providing us the opportunity to present our data and the benefits and risks of etoricoxib and rofecoxib. We recognize that the safety of this class of medicines is an important public-health issue and, as we have heard over the past two days, there are many patients in need of effective therapies for their pain. We hope that the data that we included in our background package and the presentations have helped the committee in its deliberations.

When Merck made the decision to voluntarily withdraw Vioxx from the market, we stated that we believe that it would have been possible to continue to market Vioxx with labeling that would have incorporated the data from the APPROVE.

We concluded, however, that, based on the science available at that time, a voluntary withdrawal of the medicine was the responsible course to take given that there were alternative therapies and the questions raised by the data.

Since that time, the science has continued to evolve and new data on

some of those alternate therapies have become available including the data that we have seen in this past week. Given this new information, it appears that the cardiovascular risk observed and approved is not unique to Vioxx.

We believe that the data suggest a class effect but the size of the class is uncertain.

We believe that MEDAL is an important study to address the important question on the relative risk of COX-2 inhibitors versus traditional NSAIDs. As Dr. Packer said, studies with a sufficient number of endpoints are needed. The planned C.V. analysis will provide data on greater than 600 events, of which will be in the 18- to 36-month time interval. The importance of the study is shared by the steering committee for MEDAL study who, in a letter sent to Merck this week, support the continuation of this trial.

We look forward to the deliberations of the committee on the questions before then and, as Dr. Kim stated last night, if the committee and the FDA conclude that the benefits of this class of medicines outweigh the risks (microphone turned off.)

DR. WOOD: Next?

## **Novartis**

DR. ORLOFF: Thank you for the opportunity to comment. My name is Dr.

John Orloff and I represent Novartis Pharmaceuticals.

We would like to make some general comments on how we might move forward.

While it is reasonable to consider these drugs as a class, we believe there are substantial differences in their profiles that deviate from an attempt to ascribe all follow-on their benefits and risks to a single unifying mechanism.

For example, the apparent cardiovascular risks, as noted by Dr. Fleming and others in the discussion yesterday, do not seem to correlate well with COX-2 selectivity in the clinic. More specifically, some of the agents at the highest cardiovascular risk may not be the most COX-2-selective. In addition, there are significant differences in blood-pressure profiles and in cardiorenal profiles including edema and congestive heart failure as we have shown in TARGET, a trial that enrolled over 18,000 patients.

In TARGET, significantly smaller changes in blood pressure were observed for lumiracoxib relative to either naproxen or ibuprofen.

Furthermore, the strength of the G.I. outcomes data varies considerably across agents, a benefit that is central to the assessment of benefit:risk profiles of COX-2 inhibitors. For lumiracoxib, an unequivocal reduction in G.I. ulcer complications of 79 percent was shown in TARGET and, in response to comments made yesterday, it should be noted that subgroup analyses of patients at higher G.I. risk demonstrated that the magnitude of this effect, about 70 percent, was similar to that observed in the overall population.

Thus, the benefit:risk profiles vary by drug, by dose and by exposure. Accordingly, each agent should be judged individually on its own merits.

So how do we go forward? We believe it is reasonable to consider, for any particular indication, restricting the duration of use to a time frame that is supported by the data and that this should be accompanied by a robust risk-management plan including firm postmarketing commitments.

Thank you.

DR. WOOD: Thank you. Oh; there is more.

## ***Bayer***

DR. PEITLER: Erica Peitler, Senior Vice President, Bayer Healthcare, Global Head of R&D. Bayer was pleased to have had the opportunity to share safety information on naproxen.

Important points have been made regarding naproxen in both large observational datasets as well as large randomized clinical controlled trials.

We welcome the scientific debate and dialogue on our products. We believe

that it helps to build trust and confidence in both the products, the industry and well as our company.

We appreciate the presentations today specifically on the ADAPT trial as well as the clarifying questions and comments put forth by this committee regarding how this study may have caused significant physician and consumer confusion.

Lastly, and most importantly, Bayer is committed to its consumers and its Aleve brand which contains naproxen and believes that, when used according to label directions, Aleve is a safe and effective pain reliever that offers millions of consumers an important treatment option for over-the-counter pain relief.

Thank you.

DR. WOOD: Thanks very much.

## Presentation Slides

Note: Some of the slides presented may not be included below.

### Pfizer



#### Celecoxib Benefit-Risk Summary

- Most studied anti-inflammatory agent for arthritis
- Efficacy demonstrated in OA, RA, acute pain, and FAP
  - Most common daily dose 200 mg
- Demonstrated reduction in gastropathy compared to NSAIDs
- Minimal effect on blood pressure
- CV risk not seen in arthritis settings
  - Observational studies
  - 40,000 patient meta-analysis
- CV risk increased in APC, 800 mg > 400mg, vs. placebo
- CV risk not increased in pre-SAP 400 mg vs. placebo
- CV risk not increased in ADAPT 400 mg vs. placebo

### Merck



**Other Sponsors**



**Committee Members & Other Commenting**

