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Quick Pulse

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NIH and FDA Officials Discuss the Safety of Cox-2 Inhibitors

NIH Director Dr. Elias Zerhouni, Acting FDA Commissioner Dr. Lester Crawford, and Dr. Ernest Hawk (the new Director of the National Cancer Institute's Office of Centers, Training, and Resources), and other regulatory officials hosted a conference call with reporters Friday afternoon to discuss the National Cancer Institute's decision on December 16, 2004, to halt a trial of Pfizer's Cox-2 inhibitor Celebrex (celecoxib) due to an excess of cardiac adverse events. The Adenoma Prevention with Celecoxib (APC) trial compared two doses of Celebrex (200 mg BID and 400 mg BID) to placebo. It had been ongoing for an average of 33 of the planned 60 months.

Another Celebrex trial in colorectal cancer prevention was allowed to continue – if patients and doctors decide they still want to participate. That trial, which has the same DSMB and utilized the same analytic method, found no increased cardiovascular risk with Celebrex. However, officials urged doctors and patients to review the use of Celebrex in that and every other trial on a case-by-case basis, and, if Celebrex is continued, they advised using the lowest possible dose.

The APC trial findings were the result of a new analysis initiated as a result of Merck's withdrawal of Vioxx (rofecoxib) on September 30, 2004. Dr. Zerhouni explained that DSMB for the APC trial met every six months, but given the raised concern of cardiovascular side effects with Cox-2s "seen in observational and experimental data with Vioxx," the APC trial took a number of steps to ensure the safety of the trial, including:

- Adding cardiovascular expertise to the existing DSMB. Dr. Zerhouni said, "We solicited involvement of cardiovascular experts to independently look at the data in association with the DSMB…That involved verification of events – of every potential cardiovascular-related event…and a detailed, specific analysis that mirrored the cardiovascular analysis in the Vioxx trial."
- Conducting a more focused analysis that culminated with the replication of a Vioxx-type analysis.

Dr. Zerhouni also called for an immediate review of the entire NIH grant portfolio for studies using any drug in the Cox-2 inhibitor class. He said, "I've ordered a full review of all NIH studies involving this class of drugs…Several of these reviews were ongoing since their setup…We are now advising all investigators and asking them to contact patients and assess the risks of each trial…and for investigators to analyze the data in light of this new information – and for IRBs to assess the new information and conduct a safety review as well." An estimated 40 Celebrex trials are ongoing that will be affected by this review, but most of them were described as "very small, Phase II trials designed to prove additional efficacy, laying the premise for larger trials."

Safety Analysis of APC Trial

Measurement	Placebo	Celebrex 200 mg BID	Celebrex 400 mg BID
Composite of cardiovascular death/MI/stroke	0.9%	2.2%	3.0%
CV death/MI/stroke events	6 events	15 events	20 events
Increased risk vs. placebo	---	2.5 fold ($p<.05$)	3.4 fold ($p<.05$)

Safety Analysis of PRECEPT Trial

Measurement	Placebo	Celebrex 400 mg QD
Composite of cardiovascular death/MI/stroke	1.8%	1.7%
CV death/MI/stroke events	11 events	16 events
Increased risk vs. placebo	---	Nss

The FDA did not acquit itself well on this call. The Agency did not appear in control. Dr. Crawford said the FDA has not decided what to do about Celebrex yet – e.g., to add a black box or to withdraw it from the market. He indicated the Agency would be studying the data and expects "to have more announcements in the next few days." But he refused even to say the FDA would request that Pfizer stop direct-to-consumer advertising until the FDA makes a decision. Dr. Crawford said:

- "These are important findings…FDA has seen only preliminary results. We will obtain all available data on these and other celecoxib trials and determine the appropriate regulatory action. While we have not seen all the available data, these findings are similar to the recent results of a study of Vioxx…Another drug in the class, Bextra (Pfizer, valdecoxib), has shown increased risk in patients following cardiovascular surgery."
- "Physicians should consider this evolving information in evaluating the risk of Celebrex in individual patients… The FDA advises consideration of alternative therapy. If physicians decide this is worth continuing, we advise using the lowest dose." Another FDA official added, "That is why we recommend physicians carefully evaluate whether alternative therapies fit better or whether staying on Celebrex makes more sense…And if staying on Celebrex makes sense, we recommend the lowest effective dose for that patient."
- "Patients who are taking Celebrex who have concerns should discuss them with their physicians." Since Celebrex was approved by the FDA in 1998, about 27 million Americans have taken it.
- "Since other drugs have not been studied, it is not known whether other NSAIDs pose a similar risk."
- "FDA will provide more information as it becomes available."
- Asked why the FDA isn't simply taking Celebrex off the market, Dr. Crawford said, "We just got the information last night...We are processing it…We are leaving open all regulatory options, but we don't have a decision yet on the fate of the product…We have great concerns about this product and the class. We are telling consumers two things:

  1. Check with your physician if you are taking it.
  2. Doctors should consider alternative forms of therapy if – in their medical judgment that is indicated. We will have more to say in a couple of days after we have processed the data and evaluated it."

Other key points officials made during the conference call:

The other Celebrex prevention trial. No increased cardiovascular risk was found in this trial, which is sponsored by Pfizer, not the NCI. The NCI's Dr. Hawk said, "We don't have a specific role in it…but because the cohort is similar, they employed the same sort of cardiovascular risk assessment process in their trial and found no elevated risk in that study. They were using a slightly different schedule – 400 mg/day – but that is the extent of my knowledge of that trial."

On what to do with the other ongoing Celebrex trials. NIH is notifying investigators, IRBs, and DSMBs of the new findings and requiring them to modify the informed consent, but leaving the decision on further steps up to them and the patients. Dr. Hawk said, "That is an individual decision to be made by each study. It is important to remember that this drug is used for a variety of indications and is being evaluated in a variety of different cohorts – like cancer therapy, where the risk:benefit may be different than this trial." Another official said, "We plan to offer the analytic strategy that we used here…to confirm or refute the data."

On the planned February 2005 FDA Advisory Committee meeting on Cox-2 inhibitors. Dr. Crawford said, "We will not wait to take action until the Advisory Committee meeting takes place if it is indicated medically…We are evaluating that now, and we may be making some statements very soon with respect to Cox-2s in general and this product in specific." Dr. John Jenkins, Director of the FDA's Office of New Drugs, added, "We are formulating the planning and questions. Clearly, given the new information last night on Celebrex, we will have to re-engineer some of the focus of that meeting, and potentially the questions…We have not ruled out the possiblity of regulatory action being taken by FDA in advance of that meeting, but we will be interested in reviewing all the data on Cox-2s at that meeting and hearing input from experts."

On why the FDA didn't discover this safety issue on its own. Dr. Crawford said, "The science just came forward… The shoe that drops depends on the analysis of that data…The spontaneous reporting system is not designed to detect small differences in common adverse events. It doesn't have the power to do that…The main way to do that is exactly this way – through randomized, controlled clinical trials, not stumbling on it…That is how the system finds them. For Celebrex, there was a large database and no signal plus multiple studies, including CLASS and epidemiologic studies, none of which suggested increased risk, including a Kaiser study, which suggested a possible protective effect. These are new findings …and not to be lost is that the other trial in colorectal cancer prevention, which is similar to the trial that was stopped, has not seen this…We need to evaluate this, and put all the pieces together." Dr. Jenkins added, "It is not surprising that these (findings) were found in a prevention trial because you can't do trials this large or randomized trials with a placebo in (arthritis) patients…This is how drug development, drug approval, and post-marketing is done not only in the U.S. but in other countries as well…These (APC) findings are not consistent with the other data from (Celebrex trials)."

On limiting advertising of Cox-2 inhibitors. Dr. Jenkins said, "We've made no determination yet…because we have not fully evaluated the data…Those things are among the items we might consider, but we are not ready to make a judgment…That could be considered but there is no determination at this point."

On the risk with other NSAIDs. Dr. Jenkins said, "With symptomatic patients it is very difficult to do randomized clinical trials of sufficient duration to detect a signal…That is why the Vioxx and Celebrex signals came out of prevention trials where it is ethical and practical to randomize patients to placebo for a long time…We don't have the data to rule out the cardiovascular risk of older NSAIDs. Their major risk has always been GI bleeding, hypertension, and kidney effects."

On FDA internal staff opinions about Celebrex. Unlike Vioxx, there do not appear to be any "whistleblowers" who are likely to come forward and say they warned the agency that Celebrex was unsafe. Dr. Jenkins said, "I'm not aware that anyone inside FDA had raised considerations prior to (December 16, 2004)…Obviously, we had been reviewing the cardiovascular data for all Cox-2s carefully. We actually had an internal briefing for all Cox-2s last week, and I'm not aware of anyone who raised a specific concern about the safety of Celebrex."

Pfizer wasn't the only pharmaceutical company to announce bad news on December 17, 2004.

AstraZeneca's Iressa (gefitinib). A 1,692-patient post-marketing trial, ISEL, found that overall survival of lung cancer patients was no better with Iressa than with placebo. AstraZeneca officials conceded that patients should consider Genentech/OSI Pharmaceuticals' competing drug Tarceva (erlotinib), which has shown a survival benefit in lung cancer. The company is in discussions with regulators around the world, but plans to provide Iressa for now to patients who want to continue the treatment.

Asked what the FDA plans to do about Iressa, Dr. Crawford said, "Upon approval, we required a post-approval study on the efficacy of the product. The company has now reported back to the FDA subsequent to that, and told us the product appears not to have the hoped for efficacy. So, we are evaluating that and will have a statement in the next few days."

AstraZeneca's Crestor (rosuvastatin). In March 2004, Public Citizen filed a petition with the FDA asking the agency to withdraw Crestor from the market charging the drug causes an excess of kidney damage, kidney failure, and rhabdomyolysis. The FDA is supposed to respond to this type of petition within six months, but more than nine months have passed with no FDA decision or action. Asked when a decision might be expected, officials refused to respond.

Lilly's Strattera (atomoxetine). The FDA announced that Lilly's attention deficit hyperactivity disorder (ADHD) drug was getting a new warning label to highlight the possibility that Strattera might contribute to severe liver problems in some patients and could result in death or the need for a liver transplant in a small percentage of patients. The new label advises that Strattera should be discontinued in patients who develop jaundice or laboratory evidence of liver injury.

Strattera has been prescribed to more than two million patients since the FDA approved it in 2002. As with the cardio-vascular risk with Vioxx and Celebrex, the liver problem with Strattera was not evident during the pivotal registration trials, which involved 6,000 patients. Lilly agreed to send a Dear Doctor letter to physicians warning them about the liver danger. The label for Strattera also is being revised to include a **boldface** warning, and the package insert is being updated.

Dr. Jenkins said, "(The Strattera jaundice) was reversible, and there were no deaths, but we wanted to make patients and physicians aware of that potential risk."

Congressional reaction to the Celebrex news was swift:

- Sen. Charles Grassley (R-IA) reportedly issued a statement saying the public has been left wondering when the next shoe is going to drop and creating a situation that undercuts the credibility of the FDA. FDA officials declined to respond to Sen. Grassley's comments.

- The House Energy and Commerce Committee already has demanded documents from Pfizer relating to Celebrex, giving the company until January 4, 2005, to produce them. Rep. Joe Barton (R-TX) and Rep. John Dingell (D-MI) wrote:

  "We are concerned about public representations made by the company touting the safety of Celebrex during the Fall of 2004, when the cardiovascular data in these two long-term Celebrex trials was being analyzed. For example, on November 4, 2004, the company issued a press release entitled 'Pfizer Affirms Celebrex Safety,' in which the company responds to a Canadian newspaper article that reported on voluntary spontaneous reports of cardiovascular adverse events in people taking Celebrex. We are interested in learning what information the company had regarding the NCI-sponsored study cardiovascular data at that time. Further, in November, Pfizer announced a labeling change to its other marketed Cox-2 inhibitor, known commercially as Bextra, which warned about potential cardiovascular risks. Given these events happening within a month or so before the announcement today that call into question the cardiovascular safety profile of Celebrex, we are interested in learning when and why the company chose to have a DSMB monitoring cardiovascular adverse events in Celebrex trials."

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