FDA Now Reviewing Panel's Nod to COX-2s

Celecoxib garnered nearly unanimous support; vote was more divided on rofecoxib and valdecoxib.

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GAITHERSBURG, MD. — A joint advisory panel of the Food and Drug Administration supported keeping all three approved selective cyclooxygenase-2 inhibitors on the U.S. market, with nearly unanimous support for celecoxib but far narrower votes for rofecoxib and valdecoxib, reflecting the strength of the data on the cardiovascular risks seen with those two drugs.

At the unprecedented 3-day joint meeting of the FDA's Arthritis Drugs and Drug Safety and Risk Management advisory committees, all 32 panel members agreed that, based on the available data, the three COX-2–selective NSAIDs approved in the United States significantly increase the risk of cardiovascular events, although to varying degrees, with the greatest risk evident for rofecoxib (Vioxx), voluntarily withdrawn from the U.S. market by Merck & Co. in September.

Alastair Wood, M.D., the panel chair, in summarizing the issues the panel faced before the questions were addressed, said there are now several randomized controlled trials showing significant cardiovascular risks associated with the three approved COX-2–selective NSAIDs—celecoxib (Celebrex), rofecoxib, and valdecoxib (Bextra)—which is a "far larger randomized safety signal than we've seen with any of the drugs that have been withdrawn [by the FDA] for safety reasons."

The panel members agreed that celecoxib appeared to have the lowest risk and voted 31-1 that its overall risk-benefit profile supported continued marketing for the current indications in the United States.

For the other two COX-2 inhibitors, for which evidence of this risk was much stronger, the vote was divided, with rheumatologists tipping the balance toward support of the drugs' continued marketing. For rofecoxib, the panel voted 17-15 that the overall risk-benefit profile supported marketing the drug but recommended eliminating the highest dose (50 mg), restricting the dose to the lowest available dose (12.5 mg), and limiting rofecoxib to short-term use only.

For valdecoxib, the panel voted 17-13, with 2 abstentions, in favor of keeping it on the market, with a contraindication against use of the drug in cardiac surgery patients, based on study findings of substantially increased risk of coronary events in coronary artery bypass graft (CABG) patients.

Several panelists recommended against using valdecoxib for more than 6 months, because there are no data available on this drug for longer durations. And several said it should be considered a second-line drug.

The Food and Drug Administration usually follows the advice of its advisory panels. What the committees made clear was that these drugs "should not be as widely used" and should be used only in more carefully selected patients, in whom the benefits would outweigh the risks, said John Jenkins, M.D.

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The FDA will review the panel's recommendations and expects to make final decisions about how to proceed within weeks, and will publicly announce the changes before they are implemented, said Dr. Jenkins, director of the FDA's office of new drugs, at a press briefing after the meeting.

Although the close votes for rofecoxib and valdecoxib are "challenging to interpret," the agency will closely consider the comments of the panelists, he added.

In addition to withdrawing the drugs or adding a black box warning to the drugs' labels, the FDA's other options include changing the indications of the COX-2 selective NSAIDs to second-line drugs, adding contraindications in selected patient populations, and requiring a patient medication guide to be dispensed with all prescriptions.

Short of taking a drug off the market, some form of restricted-distribution program is another option, which is in place for drugs such as thalidomide and the antipsychotic clozapine (Clozaril). Although the FDA does not have the authority to ban pharmaceutical advertisements, a black box warning makes it difficult to advertise a drug directly to consumers because of requirements for disclosing information about a drug's negative effects.

During the press conference, Dr. Wood, the committee chair, who was among those voting against keeping rofecoxib and valdecoxib on the market, said that essentially, the panels provided a "clear ranking" of the drugs.

The uniform vote to keep celecoxib on the market and the split votes regarding rofecoxib and valdecoxib reflected the clear hazard seen with those two drugs.

Commenting on celecoxib specifically, Steven Abramson, M.D., professor of medicine and pathology and director of the department of rheumatology at New York University said, "While I tend to think there is a cardiovascular signal that is COX-2 dependent, this is the weakest."

Cardiologist Steven Nissen, M.D., of the Cleveland Clinic Foundation, agreed, adding that the risk with celecoxib appeared to be dose dependent. Although there was no evidence of a cardiovascular risk signal associated with the 200-mg dose used in the vast majority of patients, the evidence of an increased risk came from the polyp-prevention trial, in which higher doses—400 mg/day and 800 mg/day—were used, he pointed out. The 800-mg dose was "very likely" to produce an excess risk, which was "probable" at the 400-mg dose, he said, advocating a black box warning of a dose-dependent increase in cardiovascular risk with this drug.


JAMES REINAKER

Dr. Steven Abramson (left) and Dr. Steven Nissen agree that among the COX-2s, celecoxib appears to have the weakest risk for cardiovascular events.

The data were considered more compelling for rofecoxib. Dr. Nissen, who voted against supporting the marketing of rofecoxib, except possibly under a compassionate use program, said the evidence of risk for rofecoxib raised more concerns.

He referred to blood pressure increases and a signal for heart failure "clearly" outside those of other drugs in the class demonstrated in the Adenomatous Polyp Prevention on Vioxx trial, at a daily dose of 25 mg—effects not seen at lower doses of celecoxib.

Compared with celecoxib and rofecoxib, there is much less information on valdecoxib, with data from only two trials available. Dr. Wood said he was uncertain whether the available data supported continued marketing of valdecoxib, which has a clear risk and no evidence of GI benefit. Referring to comments made at the meeting about patient choices, he said "it seems highly improbable" that valdecoxib is safer than celecoxib, given the size of the signal in the CABG study.

The panel agreed that some type of warning should be added to the labels of the more than 20 nonselective NSAIDs approved in the United States, for which safety has not been studied in long-term, large, placebo-controlled trials like those done for the COX-2–selective drugs.

However, several panelists recommended against using the same warning for all nonselective NSAIDs, given that naproxen as a comparator in trials seemed to do better than many of the other such drugs.

But there is still more to be learned about the traditional NSAIDs' safety, cautioned Dr. Wood, professor of medicine and pharmacology at Vanderbilt University, Nashville. However, the available data suggest that "naproxen is more beneficial than some of the others," but it is associated with GI risks, so patients using naproxen could take a proton pump inhibitor (PPI).

There are not many data on naproxen given with a PPI, but there are "certainly data in other settings" supporting this approach, he noted.

At the meeting, Garret FitzGerald, M.D., professor of cardiovascular medicine at the University of Pennsylvania, a guest speaker for the FDA, said that given the pharmacoepidemiology and the body of evidence from clinical trials, "most rational people would accept a class-based mechanism" for these drugs.

He said that in five placebo-controlled trials with three structurally distinct COX-2 inhibitors, an increase in MI and/or stroke has been documented. ■

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