Valdecoxib's Comeback Is Slim

COX-2s *from page 1*

black box warning about serious cardiovascular and gastrointestinal risks to be added to the labels of all prescription NSAIDs, including celecoxib (Celebrex). The FDA has also called for stronger warnings about potential gastrointestinal and cardiovascular risks to be added to the packages of nonprescription NSAID products. Aspirin is exempt from label revision because of its proven cardiac benefits.

"I am not surprised by this decision, but I am disappointed for my patients and the millions of others who have pain and arthritis," said John Cush, M.D., a member of FDA's arthritis drugs and drug safety and risk management advisory committee and chief of rheumatology and clinical immunology at Presbyterian Hospital of Dallas. "It seems their welfare is being put on the back burner. This will definitely have a chilling effect on patients and their doctors who need to use COX-2 drugs or NSAIDs."

He added that including all NSAIDs in the picture may result in unforeseen consequences. "The implications of this announcement on over-the-counter NSAIDs have not been delineated but may be significant."

In asking Pfizer Inc. to remove valdecoxib, the FDA went against the recommendation of its own advisory board.

In February, the committee voted 17-13 to keep valdecoxib on the market, with a contraindication against its use in cardiac surgery patients.

During a press conference announcing the agency's decisions, Steven Galson, M.D., acting director of FDA's Center for Drug Evaluation and Research, said that valdecoxib's "unique risk" of severe, life-threatening skin reactions—including toxic erythema necrolysis, Stevens-Johnson syndrome, and erythema multiforme—swayed the FDA's decision.

'Many of us feel [the FDA] ... overreacted to the issue. To have nonclinicians outweigh clinicians on a clinical matter is inappropriate.'

The agency generally follows its committees' recommendations, and this apparent turnabout rankles rheumatologists. "The FDA did not follow the advice of the committee, and many of us feel they have overreacted to the issue. To have nonclinicians outweigh clinicians on a clinical matter is inappropriate. The process could definitely use some improvement," Dr. Tindall said in an interview.

John K. Jenkins, M.D., director of FDA's Office of New Drugs, said that adverse event reports have risen since 2004, when the FDA instituted a black box warning on valdecoxib for skin reactions. He didn't release any numbers, but he said they are "significant."

"This information is fraught with uncertainty. It's very difficult to be precise with the numbers, but we think it's clear that the reports [of skin reaction] with Bextra are significantly higher than reports from other products," he said during the press conference.

Despite disagreement with the FDA recommendations, Pfizer did comply with the U.S. market withdrawal, and, in response to requests by European regulators, has also suspended sales in the European Union. The drug has also been withdrawn from the market in Canada and China.

Pfizer will "explore options" that might allow the resumption of sales, according to a statement released by the company.

However, the chance that valdecoxib could make a market comeback look slim, given comments made by Dr. Jenkins. "The path forward—if there is to be one—would have to address the question of bringing the risks and benefits into balance. But these skin reactions are unpredictable, and so it's hard to manage the risks, because you don't know who is at risk."

The future may hold even more restrictions on NSAIDs. "This is unlikely to be the last word you will hear on these drugs. Investigation continues, and in our new spirit of keeping the public informed earlier, we may be providing more recommendations as new information comes to light."

Celecoxib appears safe for the time being; Dr. Jenkins said its risk-benefit profile is satisfactory. But the agency wants a large, long-term randomized controlled safety trial of the drug.

"We have asked Pfizer to make a post-marketing commitment to evaluate Celebrex," Dr. Jenkins said. "There are several studies currently available that show conflicting results. We think it's very important to do a new, well-designed study to nail down whether Celebrex has a unique risk."

So far, the FDA has stopped short of asking other NSAID manufacturers to perform additional studies, but it has asked them to review all available safety data from both short- and long-term studies and look for additional safety signals. Because the NSAIDs' cardiovascular risks appear to be a class effect, there are not enough data to draw absolute conclusions about any differences among the individual drugs' risks, nor to rank the drugs in order of safety, Dr. Galson said.

The FDA has no intention of removing any over-the-counter NSAIDs from the market, he added.

Pfizer announced plans to reimburse patients for unused valdecoxib. Details on the buyback will be available on www.bextra.com. ■

Until Guidelines Are Revised, ACR's President Suggests Care Options

With the recent withdrawals of both rofecoxib and valdecoxib, pain relief options are dwindling for rheumatology patients, said Dr. Tindall.

In light of the changes and the new warnings on all NSAIDs, the American College of Rheumatology is revising its treatment guidelines for osteoarthritis and rheumatoid arthritis. Until those guidelines are finished, Dr. Tindall offers the following tips for managing patients:

► In people who have some risks for GI bleeding, ulcers, or gastritis and for whom celecoxib doesn't work or is contraindicated, use one of the older, nonselective NSAIDS, in combination with a proton pump inhibitor.

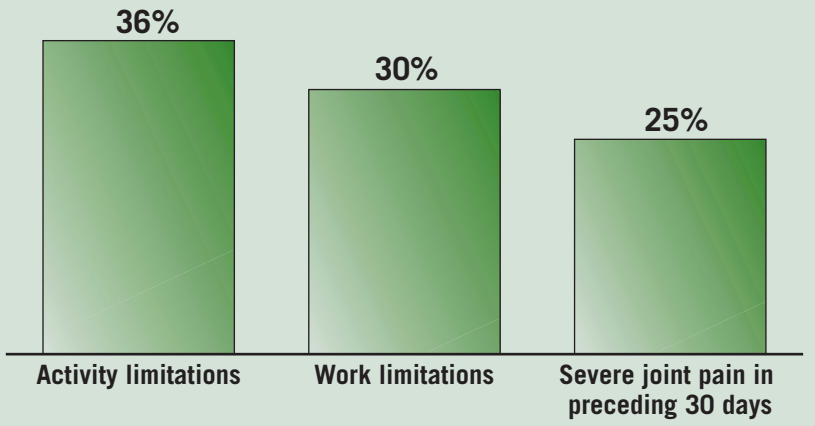
► For patients on anticoagulant therapy, select a nonacetylated NSAID, such as salsalate. "It doesn't affect bleeding times, and the incidence of peptic ulcers and gastritis is less with this. But it also isn't very potent."

► For rheumatoid arthritis patients, turn to corticosteroids, "even though patients aren't very happy with that alternative," she said. "After that, we're left with only the pure analgesics—everything from acetaminophen to morphine."

—Michele G. Sullivan

DATA WATCH

Percentage of Adults Diagnosed With Arthritis Who Reported Limitations or Pain in 2002



Note: In 2002, an estimated 42.7 million adults reported having arthritis, which includes rheumatoid arthritis, gout, lupus, and fibromyalgia.

Source: Centers for Disease Control and Prevention

Kevin Foley, Research/Angie Ries, Design

COX-2 Uproar Predicted to Alter Future Clinical Trials

BY PATRICE WENDLING
Chicago Bureau

CHICAGO — Recent events surrounding selective cyclooxygenase-2 inhibitors will have far-reaching implications for future drug trials, Gary S. Hoffman, M.D., said at a symposium sponsored by the American College of Rheumatology.

Drugs under investigation for chronic diseases such as arthritis will require longer trials and follow-up than in the past, in part because of their likely long-term use among the patients who need them.

"We can no longer endorse or not endorse these drugs based upon short-term studies, some of which have been as short as 6 weeks or 12 weeks and usually, certainly, less than a year," said Dr. Hoffman, a member of the Food and Drug Administration's arthritis advisory committee.

NSAID trials now will include cardiovascular and thrombotic events among the adverse events they monitor.

But this raises questions as to whether there are other adverse events (AEs) such as cancer, autoimmune effects, or neurocognitive dysfunction that are beyond our current knowledge, said Dr. Hoffman, professor of medicine and chair of rheumatic and immunologic diseases at the Cleveland Clinic Foundation.

"Are we looking at this with blinders on because of recent events or are there other important AEs that we should also be casting a broader net for?" Dr. Hoffman asked.

"Perhaps there are increases in malignancies if you follow patients who take drug x, y, or z long enough. How long should those patients be studied in the context of randomized trials?" he said.

Although answers to these questions are lacking, it's obvious that closer pre-market drug scrutiny will come at a greater cost, he said.

Forces such as the market, consumers, and the medical community will need to determine how cost-effectiveness will be measured, and ultimately who will pay.

New strategies need to be developed to make new drug studies cost effective, he said.

Ironically, it was adverse events associated with nonselective NSAIDs that drove the COX-2 market in the first place, he noted. Research suggests that as much as one-third of every dollar spent on NSAIDs goes to managing adverse events. ■

Pages 20a—20h