Warnings on OTC NSAIDs

COX-2 *from page 1*

empt 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 from the market, 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.

The agency generally follows the advice of its advisory committees, and it is this apparent turnabout that rankles many physicians.

"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 adverse event reports have risen since 2004, when the FDA instituted a black box warning on valdecoxib for skin reactions. He didn't release numbers, but 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.

In addition to complying with the FDA's request to withdraw valdecoxib from the market, Pfizer has also suspended sales of the drug in the European Union at the request of its pharmaceutical regulators. Valdecoxib also has 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," Dr. Jenkins said.

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, adding that FDA has no intention of removing any over-the-counter NSAIDs from the market. "I want to emphasize that our current thinking is that the over-the-counter products, taken at the recommended dose according to the instructions, are not a problem, and people don't have to be concerned about them except for the risks that are already listed and that will be added."

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

Treatment Options for Arthritis

With the recent withdrawals of both rofecoxib and valdecoxib, pain relief options are dwindling for patients with arthritis, according to 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."

Watch for Osteonecrosis With Long-Term Bisphosphonates

BY KATE JOHNSON
Montreal Bureau

Prolonged use of bisphosphonate therapy can lead to osteonecrosis of the jaw—a previously unrecognized and potentially serious complication that can often be avoided, according to Salvatore Ruggiero, M.D., D.M.D.

Patients on intravenous therapy face the highest risk whether they are taking the medication for cancer or for osteoporosis; the risk is lower, although not absent, in those taking oral bisphosphonates, said Dr. Ruggiero, who is chief of oral and maxillofacial surgery at Long Island Jewish Medical Center in New Hyde Park, NY.

"The push is to alert physicians that this is a potential problem, so that before they start a patient on bisphosphonates, they send them to a dentist to extract any teeth that are nonrestorable," he told this newspaper. "Prevention and early detection are important for preserving the jawbone."

In his experience, most cases have been associated with infections after dental surgeries such as tooth extractions. However, necrosis has also occurred spontaneously in a significant number of patients, he said.

For this reason, he recommends that all patients on long-term bisphosphonate therapy have two or three preventive dental visits per year, and that physicians be alert for early signs of necrosis.

Patients should be alert to "things like tooth pain, swelling, numbness of the lip and chin, or pain within the jaw. This is not a very difficult diagnosis to make. You basically have to look in the mouth, and if you see exposed bone it is very clear," he said.

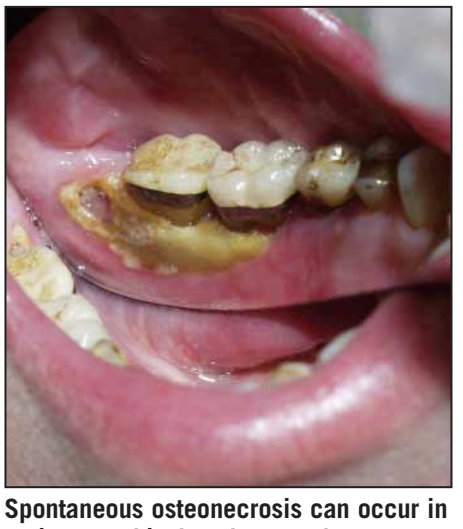
Dr. Ruggiero's published research (J. Oral Maxillofac. Surg. 2004;62:527-34) has prompted warnings from the Food and Drug Administration, as well as from Novartis, which manufactures the intravenous bisphosphonates pamidronate disodium (Aredia) and zoledronic acid (Zometa).

Novartis has also changed its package inserts to reflect this information. Labeling for oral bisphosphonates has not changed.

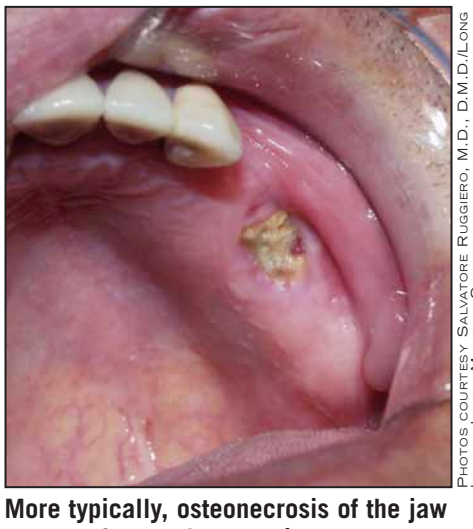
His study identified 63 patients with osteonecrosis of the jaw (ONJ), all of whom had received bisphosphonate therapy for extended periods (6-48 months). Overall, 56 of the patients had used intravenous bisphosphonates for cancer chemotherapy, and the remaining 7 for osteoporosis.

Until these cases were identified, ONJ had been a rare clinical scenario, Dr. Ruggiero noted.

The typical presenting symptoms were pain and nonhealing exposed bone at the site of a previous tooth extraction. However, nine patients (14%) had no history of a recent dentoalveolar procedure and presented with spontaneous exposure and necrosis of the alveolar bone. Biopsies of the lesions showed no evidence of metastatic disease.



Spontaneous osteonecrosis can occur in patients on bisphosphonates long term.



More typically, osteonecrosis of the jaw occurs after tooth extraction or surgery.

PHOTOS COURTESY SALVATORE RUGGIERO, M.D., D.M.D./LONG ISLAND JEWISH MEDICAL CENTER

The lesions had been refractory to conservative debridement procedures and antibiotic therapy. Most patients required surgical procedures to remove all of the involved bone, which included 45 sequestrectomies, 4 marginal mandibular resections, 6 segmental mandibular resections, 5 partial maxillectomies, and 1 complete maxillectomy.

Despite these surgical procedures, five patients had persistent bone necrosis and developed new regions of exposed bone even after they stopped bisphosphonate therapy.

Dr. Ruggiero speculates that the impaired bone wound healing may result from a compromised vascular supply caused by the antiangiogenic effects of bisphosphonates. The lack of bone problems elsewhere in the body may be due to the unique environment created by oral microflora. ■