

Celecoxib Gets New Indication, New Warning

Drug is now approved for ankylosing spondylitis, but black box highlights risk of MI and stroke.

BY ALICIA AULT
Contributing Writer

Celecoxib, the only cyclooxygenase-2 inhibitor left on the U.S. market, has won an additional approval from the Food and Drug Administration—but, as expected, the drug also received a black box warning on the increased risk of cardiovascular events.

The Pfizer Inc. drug was approved for ankylosing spondylitis (AS), a connective tissue disorder causing inflammation of the spine and large joints that affects about 400,000 Americans, primarily between the ages of 20 and 40 years.

The new warning, a result of an FDA advisory committee's recommendations in February, says that celecoxib (Celebrex) may increase the risk of "thrombotic events, myocardial infarction, and stroke, which can be fatal." The risk may increase with duration of use, according to the warning. The drug is also contraindicated for treating post-coronary artery bypass graft surgery pain.

The black box warning also highlights an increased risk of "serious gastroin-

testinal adverse events, including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal."

Rheumatologists said that despite the warnings, they would use celecoxib, when appropriate, in treating AS. According to the drug's label, in two placebo- and active-controlled trials, celecoxib was statistically superior to placebo (at doses of 100 mg twice daily, 200 mg once daily, and 400 mg once daily) in global pain, global disease, and functional impairment.

Theodore Fields, M.D., of Weill Medical College of Cornell University, noted that it's preferable to start patients on analgesics, but that if there's swelling, anti-inflammatories often have to be used. There are a number of "patients with ankylosing spondylitis where it makes sense, in spite of the known risks, to give them NSAIDs or COX-2s," said Dr. Fields, who is also clinical director of the Early Arthritis Center at the Hospital for Special Surgery in New York.

The struggle sometimes comes in deciding between celecoxib or an NSAID such as naproxen, said physicians.

John Reveille, M.D., professor of medi-

cine and director of rheumatology at the University of Texas Health Science Center in Houston, said he'd use celecoxib in patients who have a gastrointestinal intolerance to other NSAIDs.

Dr. Fields prefers to use celecoxib in patients who have a higher than average risk of GI complications, but lower than average cardiovascular risk.

Theoretically, because AS patients tend to be younger, the risk of cardiovascular complications is lower, Dr. Fields said in an interview. But, there's also some evidence that patients with inflammatory conditions, such as lupus and rheumatoid arthritis, are at higher risk for atherosclerosis, he said, adding that although the same has not been proven for AS, it is hypothetically possible.

Both Dr. Fields and Dr. Reveille said they'd avoid using celecoxib in patients who have cardiovascular disease or who may be at higher risk—those who are older, male, diabetic, or hypertensive. Neither rheumatologist is a paid consultant for any drug makers.

The new Celebrex label recommends that it be prescribed at the lowest effective dose for the shortest duration. For AS, the recommended dose is 200 mg daily; if there is no response after 6 weeks, the dose should be titrated to 400 mg daily, ac-

cording to Pfizer. If there is still no response after 6 weeks on that dosage, other treatment options should be considered.

Dr. Fields said he starts patients on 200 mg daily, which he says "is a dose that can be anti-inflammatory." Dr. Reveille begins patients on a dosage of 100 mg daily and moves up to 200 mg if there is no response.

Both say that patients have become more nervous about using celecoxib than have physicians.

That does not mean rheumatologists have no concerns. "There's no question that I'm watching patients more closely, talking to them about it, and asking if anything new has evolved in their history," Dr. Fields said, adding that he regularly monitors patients for cardiovascular signs and always considers whether it's possible to shorten therapy or make it intermittent.

Dr. Reveille said he monitors patients on any NSAID or COX-2, including running liver function and complete blood counts at least twice a year. "I don't give a patient an NSAID and see them back a year later."

AS is the sixth approved indication for celecoxib in the United States, but sales have dropped steeply from a year ago. In the first half of 2005, worldwide celecoxib sales totaled \$813 million, a decline of 46% from the previous year. ■

Methylnaltrexone Relieves Opioid-Induced Constipation

BY JANE SALODOF MACNEIL
Southwest Bureau

ORLANDO — Single injections of methylnaltrexone relieved opioid-induced constipation in 4 hours for 60% of hospice and palliative care patients in a randomized, placebo-controlled phase III trial.

The earliest responses occurred within 5 minutes, and most patients responded within 2 hours, investigator Jay Thomas, M.D., reported at the annual meeting of the American Society of Clinical Oncology. The patients in the trial had not had a bowel movement for at least 48 hours prior to treatment, despite being on a stable laxative regimen for at least 3 days.

Dr. Thomas, clinical medical director of the San Diego Hospice and Palliative Care Center, reported that the single-dose trial enrolled 154 patients with advanced medical disease from 16 hospices. Of the 154 patients, 123 (80%) had cancer. The population also included patients with pulmonary disorders (12), AIDS (8), amyotrophic lateral sclerosis (3), cardiovascular conditions (2), and other disorders (6).

"These patients were very sick and near the end of life," Dr. Thomas said. Since most patients lived at home, visiting nurses trained family members to give the injections in place of an enema or other rescue regimen. If the study drug did not provide relief within 4 hours, rescue was permitted.

The trial randomized patients into three groups: 52 patients were given a placebo, 57 received 0.15 mg/kg of methylnaltrexone, and 55 received 0.30 mg of methylnaltrexone/kg. Median time to laxation was

70 minutes for the 0.15-mg dose, 45 minutes at 0.30 mg, and more than 1,440 minutes (24 hours) with placebo.

Dr. Thomas, an internist, said the difference in efficacy between the two methylnaltrexone doses was negligible. "With the higher dose, you didn't get more bang for your buck," he said. "If anything, you got more side effects."

Side effects were minimal, however. The two most common adverse events, abdominal cramping and flatulence, were associated with successful laxation. The next most common side effects were nausea and dizziness.

The trial's sponsor, Progenics Pharmaceuticals Inc. of Tarrytown, N.Y., has already started a second phase III study at 30 centers to assess repetitive doses in patients with chronic constipation due to opioid painkillers. The company hopes to apply for U.S. Food and Drug Administration approval by the end of the year, Robert J. Israel, M.D., medical affairs vice president, told this newspaper.

The late Leon Goldberg, a pharmacologist at the University of Chicago, synthesized methylnaltrexone 25 years ago to help a dying friend who suffered from morphine-induced constipation. A μ receptor antagonist, it does not cross the blood-brain barrier, and therefore can act on opioid-induced constipation without blocking the pain-killing effects of opioids.

Dr. Israel said Progenics obtained the rights to develop methylnaltrexone after he read a report on a randomized trial in which the experimental drug relieved constipation in methadone patients (JAMA 2000;283:367-72).

"The market was small for end of life, so a lot of [drug companies] look at that as not attractive," Dr. Israel said. "We are a small company. That was not an obstacle for us."

Enthusiastic physicians surrounded Dr. Thomas and Dr. Israel after the presentation. "The sooner it gets to market, the better," said Lee Schwartzberg, M.D., research director of the West Clinic in Memphis, as others in the crowd suggested strategies for convincing insurance companies to provide reimbursement.

In a podium discussion of the presentation, Kathleen M. Foley, M.D., called methylnaltrexone "the palliative and pain

world's answer to a targeted therapy." Dr. Foley of Memorial Sloan-Kettering Cancer Center in New York said the investigators need to refine the dose in short-term vs. long-term opioid users, and to explore intravenous and oral delivery systems. She also suggested that methylnaltrexone might have a role in treating postoperative ileus.

Dr. Thomas predicted that drug makers would eventually be able to offer pills combining methylnaltrexone with opioid painkillers. "When someone takes OxyContin they would have methylnaltrexone in the pill, so they would never have the opioid-induced side effect of nausea, urinary retention, and constipation," he said. ■

