Celecoxib Receives New Indication, New Warning

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

According to the drug's label, in two placebo- and active-controlled trials, celecoxib was statistically superior to placebo 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 medicine 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 physician 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, according 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 celecoxib than physicians.

That does not mean physicians 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.

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. ■

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