Asthma Drug Label to Include Psychiatric Risk

BY LORINDA BULLOCK

The Food and Drug Administration last month called on manufacturers of leukotriene inhibitors to include safety precautions on their drug's labeling, because of reports of neuropsychiatric events in patients taking these drugs.

The FDA said the reported neuropsychiatric events included cases of agitation, aggression, anxiety, dream abnormalities and hallucinations, depression, insomnia, irritability, restlessness, suicidal ideation and behavior, and tremor in patients using montelukast (Singulair), zafirlukast (Accolate), and zileuton (Zyflo, Zyflo CR).

Manufacturers of these drugs were asked to submit all available clinical trial data for these products for the safety review that concluded in April.

In its review, the FDA found that some reports included clinical details consistent with a drug-induced effect.

According to an FDA update from May, most of the reports of neuropsychiatric events were associated with montelukast, which is the most commonly prescribed drug that acts through the leukotriene pathway.

In the clinical trial data submitted by the manufacturers, neuropsychiatric events were not commonly observed, the FDA said. "However, the available data were limited because the trials were not designed to look for neuropsychiatric events. Sleep disorders [primarily insomnia] were reported more frequently with all three products compared to placebo."

The FDA advises that patients and health care providers be aware of the potential for neuropsychiatric events with these drugs used to treat asthma and symptoms of allergic rhinitis. The agency also suggests that physicians discontinue treatment if patients develop neuropsychiatric symptoms. ■

More information is available at www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm079523.htm.

Difficult to Control Asthma May Be Vocal Cord Dysfunction

BY DOUG BRUNK

SAN DIEGO — About one-third of patients referred to an asthma specialty clinic who were believed to have difficult to control asthma actually had vocal cord dysfunction, results from a single-center study showed.

"If patients have been many different medicines—they've been on oral or inhaled steroids and they're not responding—it's worth checking to see if they actually have asthma or not," study coauthor Catherine Vitari, R.N., said in an interview during a poster session at an international conference of the American Thoracic Society.

Thirty-three percent of people referred for asthma didn't actually have asthma.

DR. WENZEL

In a study led by her associate, Dr. Sally E. Wenzel, a pulmonologist and the director of the Asthma Institute at the University of Pittsburgh Medical Center, the researchers reviewed the charts of 152 new patients evaluated at the institute between December 2006 and September 2008 in an effort to verify if the diagnosis of severe asthma was substantiated or not.

Of the 152 patients 119 (78%) had a presenting diagnosis of asthma while 33 had another diagnosis such as dyspnea, cough, and emphysema. All patients underwent a full evaluation.

Ms. Vitari, a clinical research nurse at the Asthma Institute, reported that 40 of the 119 patients who presented with an asthma diagnosis underwent methacholine challenges with laryngoscopy because their history and physical suggested asthma may not be the primary diagnosis. Of these 40 patients, 39 had a negative test, which precluded the diagnosis of asthma in 33% of the 119 patients. "We didn't expect to see this," she commented. "That's a pretty high percentage of people referred for asthma who didn't actually have asthma."

She also noted that four of seven patients who presented with a diagnosis of cough, which may indicate asthma, had methacholine challenges with laryngoscopy that showed vocal cord dysfunction; the three other patients were diagnosed with vocal cord dysfunction based on their exam and testing.

Ms. Vitari noted that it's Dr. Wenzel's practice to perform a laryngoscopy at the time of the methacholine challenge "to see if the vocal cords are closing or spasming, indicating vocal cord dysfunction, or if it's truly asthma," she explained. "If you think it's vocal cord dysfunction and you send the patient to ENT instead to do a laryngoscopy and they don't see anything, it could be that the vocal cord dysfunction isn't acting up at that time since the spasms can be episodic and/or related to triggering events/stimuli."

She acknowledged certain limitations of the study including its single center design and the fact that only one physician did the assessments. The researchers had no conflicts to disclose. ■

Pirfenidone May Slow Deterioration From Pulmonary Fibrosis

BY DOUG BRUNK

SAN DIEGO — Results of two phase III studies of pirfenidone, an oral antifibrotic and anti-inflammatory agent, have shown that the drug could slow the deterioration of lung capacity in patients with idiopathic pulmonary fibrosis.

The 72-week-long trials, known as CAPACITY 1 and CAPACITY 2, enrolled 779 patients at 110 sites in 11 countries.

"The findings of the CAPACITY trials, coupled with the results of the phase II and phase III studies in Japan and the urgent unmet medical need, suggest that pirfenidone may provide a meaningful clinical benefit in patients with IPF," trial cochair Paul Noble said during an international conference of the American Thoracic Society.

Manufactured by InterMune Inc., pirfenidone is currently approved in Japan for the treatment of IPF. InterMune expects to submit a New Drug Application for the agent to the Food and Drug Administration in the summer of 2009.

Patients were eligible for the studies if they had a diagnosis of pulmonary fibrosis confirmed by CT scan or by biopsy and if they had a forced vital capacity (FVC) that was 50% of predicted value or greater and a diffusing capacity of the lung for carbon monoxide that was 35% of predicted value or greater.

The 344 patients in CAPACITY 1 were randomized to receive pirfenidone 2,403 mg/day or placebo for 72 weeks, while the 435 patients in CAPACITY 2 were randomized to receive either pirfenidone 2,403 mg/day, pirfenidone 1,197 mg/day, or placebo for 72 weeks. The primary end point was change in percent predicted FVC from baseline to week 72.

The mean age of patients in CAPACITY 1 was 68 years, while the mean age of CAPACITY 2 patients was 67 years, said Dr. Noble, professor of medicine and chief of pulmonary, allergy, and critical care medicine at Duke University, Durham, N.C.

In CAPACITY 2, patients in the treatment group achieved a significant reduction in change in percent predicted FVC at week 72, compared with placebo (–6.49% vs. –9.55%, respectively), and an increase in progression-free survival time (hazard ratio of 0.64). The treatment group also demonstrated a favorable effect on change in FVC category ($P = .001$).

In CAPACITY 1, there was no significant mean change in percent predicted FVC at week 72 between the treatment and placebo groups (–6.49% vs. –7.23%, respectively), but there was evidence of a treatment benefit at each assessment through week 48. "CAPACITY 1 did not achieve statistical significance on the primary end point," Dr. Noble said. "However, results were generally consistent with and supportive of CAPACITY 2."

According to a prepared statement from InterMune, a pooled analysis of categorical FVC change from the two studies "showed that 30% fewer patients experienced a 10% or greater decrease in FVC at week 72 in the pirfenidone group than in the placebo group. This magnitude of decline is considered clinically meaningful, as a 10% decline in percent predicted FVC has been shown in multiple studies to be an independent predictor of mortality in patients with IPF. In addition, 40% more patients in the pirfenidone group did not experience a decline in percent predicted FVC at week 72 versus baseline compared to those who received placebo."

At the meeting, Dr. Noble reported that the pattern of adverse events in both trials was generally comparable to those observed in previous clinical studies of pirfenidone. The most common adverse events in the pirfenidone group compared with placebo were nausea (35% vs. 18% in CAPACITY 2, and 38% vs. 16% in CAPACITY 1), rash (31% vs. 10%, and 34% vs. 13%), fatigue (28% vs. 21%, and 33% vs. 20%), diarrhea (25% vs. 17%, and 33% vs. 21%), dyspepsia (17% vs. 9%, and 21% vs. 6%), and dizziness (19% vs. 10%, and 18% vs. 10%).

Rash was generally mild to moderate in both studies; only two patients (one in each CAPACITY study) who received pirfenidone had a severe rash.

Researchers also analyzed the incidence of patients who died during the treatment period, which was defined as the time between receiving the first dose of treatment and 28 days after receiving the last dose. In CAPACITY 1, 5% of the pirfenidone group died during the treatment period, compared with 9% of the placebo group. In CAPACITY 2, 6% of pirfenidone patients died during the treatment period, compared with 8% of placebo patients.

"CAPACITY 2 demonstrated a statistically significant and a clinically meaningful effect on the primary end point of change in percent predicted FVC and the secondary end points of progression-free survival and categorical change in percent predicted FVC," Dr. Noble concluded. "CAPACITY 1 did not, and it failed to achieve statistical significance on the primary end point."

The studies were funded by InterMune. Dr. Noble disclosed that he has served as a consultant, steering committee member, or cochair of a steering committee for InterMune, Actelion Pharmaceuticals Ltd., Boehringer Ingelheim GmbH, and Novartis. ■