With Palladone Pulled, FDA Looks at Other Opioids

Agency, company agree that concomitant use of alcohol could cause ‘dump’ of the hydromorphone.

**By Alicia Ault**

**Contributing Writer**

Shortly after Purdue Pharma announced in July that it was taking its 24-hour opioid Palladone off the market because of a potentially fatal interaction with alcohol, the Food and Drug Administration said it was looking into the possibility that other sustained-release narcotics could pose the same danger.

The Palladone withdrawal (hydromorphone HCl extended release) came at the FDA’s request. The FDA and the company investigating whether the transdermal fentanyl patch marketed as Duragesic might contain-release opioids might pose the same risk. Both FDA and the company conducted in vitro testing of currently marketed products. The agency won’t say what those tests revealed, but the spokesperson said that based on the results, the FDA has asked “sponsors of certain products” to perform human studies to determine if there is any interaction with alcohol, and when it might occur.

The FDA actions throw yet another category of painkillers into an uncertain light.

Pain Relievers

**Drug Combination for Migraines Deemed too Risky for Approval**

**By Elizabeth Mechtie**

Senior Writer

ROCKVILLE, MD. — At a meeting last month, members of the Food and Drug Administration’s Peripheral and Central Nervous System Drugs Advisory Committee agreed that the risk of tardive dyskinesia associated with the metoclopramide component of a fixed-dose combination pill outweighed the product’s benefits for treating migraines.

All 12 panel members found that there was not enough evidence to assume that the intermittent chronic use of the product, which combines metoclopramide with naproxen, did not cause tardive dyskinesia (TD) and that it was not possible to determine a maximum number of monthly doses that could be recommended to avoid the risk of TD.

TD is a well-known side effect of metoclopramide, a neuroleptic dopamine receptor antagonist, although the incidence is unclear, said Eric B stylings, M.D., clinical team leader in the FDA’s division of neurology products, Rockville. Although no cases were reported in trials of the fixed-dose combination of 16 mg of naproxen and 500 mg of metoclopramide, which the company called MT 100, the database was too small to detect rare events, he told the panel.

In May 2004, the FDA sent the company a “not approvable” letter, stating that the company had not established that MT 100 was effective for acute treatment of migraine or that the metoclopramide component contributed to the effectiveness, and that there was no evidence to support the company’s argument that intermittent long-term use for migraines would not be associated with TD.

The advisory panel meeting was held to discuss the TD risk associated with the addition of metoclopramide, which is approved in the United States for short-term treatment of gastroesophageal reflux disease and diabetic gastroparesis. The label warns about the risk of TD, which increases with the duration of treatment but may occur after relatively brief periods of treatment at low doses.

The day after the meeting, Pozen Inc., a Chapel Hill, N.C.–based pharmaceutical company, announced in a statement that it would no longer pursue approval of the combination product in the United States, “based on a thoughtful review of the outcome” of the meeting. Contributing to the decision was the company’s plan to file an application for approval of a product to treat acute migraines, a combination formulation of sumatriptan and naproxen.

Several days later, the company announced that it had submitted the new drug application to the FDA for the sumatriptan-naproxen combination.

In two phase III trials of over 2,000 patients with moderate or severe migraine, the sustained pain response at 24 hours associated with one dose of MT 100 was 4% and 6% above the level achieved with naproxen alone (36% and 32% among MT 100 users vs. 30% and 28% on naproxen alone), which the FDA said was not significant. There were no significant differences in the 2-hour pain response. Although there were no TD cases reported in trials, the company estimated that the annual incidence of TD at a daily metoclopramide dose of 30 mg–40 mg for 72 days a year for approval of the product would be up to 0.38%. All but 1 of the 12 panelists agreed this was not a reasonable estimate; most said that the incidence was simply unknown and several others said they believed the risk was higher.

Metoclopramide enhances the absorption of naproxen and counteracts gastric stasis associated with migraines, with antidepressant and antinflammatory effects, according to Pozen.