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 same time the FDA announced it was investigating whether the transdermal fentanyl patch marketed as Duragesic might be linked to a number of deaths.

"We are investigating 120 deaths that seemingly are related to overdose," Robert Meyer, M.D., director of the Office of Drug Evaluation II at the Center for Drug Evaluation and Research (CDER), said in a statement.

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

Stamford, Conn.–based Purdue withdrew Palladone just 5 months after it was introduced to a limited number of prescribers. The FDA and the company agreed that testing showed that concomitant use of alcohol could cause a "dosage dump" of the hydromorphone. But there's a difference of opinion on what was known when.

Purdue, which also makes the oft-diverted and abused oxycodone (OxyContin) had conducted several tests to assess Palladone's susceptibility to tampering, spokesman James Heins said in an interview. In the lab, Purdue researchers used various means to cause an instantaneous release of Palladone's contents to produce euphoria. Dissolving capsules in alcohol did just that, Mr. Heins said.

A similar effect was observed when healthy volunteers were given 8 ounces of various proofs of alcohol (all the subjects were given naltrexone as a block).

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Data from these studies were given to FDA in November, several months after the drug's approval in September 2004, but before it had been formally launched, he said.

The FDA, however, said those were "preliminary" data, and that a full report was not received until February 2005. With those full data in hand, CDER officials met with Purdue again in May to discuss strengthening Palladone's warnings. But the agency decided that the risk of death from inadvertent concomitant alcohol use was significant enough that even Palladone's strict risk management plan could not prevent potentially serious adverse events or deaths, according to an FDA spokesperson.

"CDER concluded that had it been aware of the alcohol interaction prior to approval, Palladone would not have been approved," the spokesperson said in an interview.

The Purdue tests on Palladone led the agency to consider whether other sustained-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.

Extended-release product labels already warn against using alcohol simultaneously.

The removal of Palladone does not leave a huge treatment gap, although the new drug was widely anticipated because of its ease of use, said B. Eliot Cole, M.D., executive director of the American Society of Pain Educators. "There are still plenty of other medications, not just opioids, that are useful for pain control, including antidepressants, anticonvulsants, anti-inflammatory agents, and more," he told this newspaper.

Dr. Cole said warnings already contained in Palladone's label made it clear "that using alcohol with Palladone was a very bad idea." But he did not disagree with the decision to remove the drug from the market. Dr. Cole participated on an advisory board for Palladone last fall and has been a speaker for Purdue.

Neither Purdue nor the FDA received any reports of serious adverse events or deaths related to Palladone and alcohol use, and Dr. Cole said that he had not heard of any anecdotally, either.

With Duragesic, however, there have been multiple reports of potential overdoses. In June, Janssen, the Johnson & Johnson division that makes and sells Duragesic, notified health professionals that concomitant use with cytochrome P450 3A4 inhibitors could lead to potentially fatal reactions. The company also issued stronger warnings against using Duragesic with alcohol or using patches that were torn.

The FDA issued a public health advisory in July stating that it was investigating deaths related to Duragesic. It urged physicians to educate patients about signs of overdose, proper patch application, and use of other medications while using the patch, as well as proper storage and disposal of the patch. The agency said that initial reviews indicated that unintentional overdoses might be related to use of multiple patches, application of heat to a patch (which might increase fentanyl absorption), injection or ingestion of the patch contents, leaking patches, and accidental exposure to the drug by coming into contact with a discarded patch. ■

Drug Combination for Migraines Deemed too Risky for Approval

BY ELIZABETH MECHCATIE
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 Bastings, 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 metoclopramide with 500 mg of naproxen, 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 another 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 would be up to 0.038%. 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 antinausea and antiemetic effects, according to Pozen. ■