Propoxyphene Yanked Due to Arrhythmia Risk

BY LORINDA BULLOCK

FROM AN FDA TELECONFERENCE

Propoxyphene, a widely used treatment for mild to moderate pain, has been removed from the U.S. market because of an increased risk of serious fatal heart rhythm abnormalities in people taking the drug, Food and Drug Administration officials said Nov. 19.

During a teleconference, health care providers were advised to stop prescribing the drugs known by the brand names Darvon and Darvocet immediately.

"The trial showed that propoxyphene significantly increased the QT interval, which is one measure of the heart's electrical activity. This effect was seen in normal volunteers at propoxyphene doses at or slightly above the maximum recommended doses in the approved labeling," said Dr. John Jenkins, director of the Office of New Drugs at the FDA's Center for Drug Evaluation and Research (CDER).

Dr. Jenkins said that an increase in the QT interval of the magnitude seen with propoxyphene is known to increase the risk that patients may suffer potentially serious or even fatal heart rhythm abnormalities. "What is unique here is the new heart data show that adverse effects occur in regular doses in normal volunteers and not just in overdose."

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The new data from the clinical trial also showed that propoxyphene increased the duration of two other measures of the heart's electrical activity – the PR interval and the QRS complex. Increases in these measures also are known to lead to abnormalities in heart rhythm, Dr. Jenkins said.

Since 1978, two citizen petitions have asked the agency to either ban the drug or reschedule it from Schedule IV to Schedule II. The agency did not act on the petitions until July 2009, when it required the manufacturer of Darvon and Darvocet, Xanodyne Pharmaceuticals Inc., to conduct a new safety study of the drug in healthy volunteers.

The new data altered the agency's assessment of the risk-benefit profile of the drug by showing that the heart risk of propoxyphene could apply to all users and not just those who took excessive doses or those with medical conditions that might reduce their ability to clear propoxyphene from the body, Dr. Jenkins said.

"Since it is not possible to accurately predict what patients might be at risk or to monitor patients while on the drug for signs of an increased risk, we concluded that a risk evaluation and mitigation strategy or REMS would not be appropriate in this case," Dr. Jenkins said.

At the agency's request, Xanodyne voluntarily removed its drugs from store shelves Nov. 18. The FDA has requested that manufacturers of the approved generic versions of propoxyphene do the same.

In 2009, an estimated 10 million people were taking some form of propoxyphene – usually in a formulation that also contains acetaminophen (such as Darvocet), said Dr. Gerald Dal Pan, director of the FDA's Office of Surveillance and Epidemiology at CDER. Patients taking the drug are advised not to stop treatment immediately. Instead, they should discuss with their physicians safely switching to another treatment. If propoxyphene is stopped suddenly, Dr. Dal Pan said, withdrawal symptoms such as nausea, vomiting, diarrhea, anxiety, and shivering may occur. Once the drug is cleared from the body, the heart risks go away, so longtime users should not fear that they are more vulnerable to heart arrhythmias, he said.

Internationally, regulatory agencies have already banned propoxyphene. The FDA's original approval of propoxyphene in 1957 was based on older safety standards and did not include "the careful assessment of the possible effects on the electroactivity of the heart that is required for all new drugs today," Dr. Jenkins said. ■