FDA Drug Safety Communication: FDA recommends against the continued use of propoxyphene

Safety Announcement

[11-19-2010] The U.S. Food and Drug Administration (FDA) is recommending against continued prescribing and use of the pain reliever propoxyphene because new data show that the drug can cause serious toxicity to the heart, even when used at therapeutic doses. FDA has requested that companies voluntarily withdraw propoxyphene from the United States market.

Propoxyphene is an opioid pain reliever used to treat mild to moderate pain. It is sold under various names as a single-ingredient product (e.g., Darvon) and as part of a combination product with acetaminophen (e.g., Darvocet).

FDA's recommendation is based on all available data including data from a new study that evaluated the effects that increasing doses of propoxyphene have on the heart (see Data Summary below). The results of the new study showed that when propoxyphene was taken at therapeutic doses, there were significant changes to the electrical activity of the heart: prolonged PR interval, widened QRS complex and prolonged QT interval. These changes, which can be seen on an electrocardiogram (ECG), can increase the risk for serious abnormal heart rhythms. FDA has concluded that the safety risks of propoxyphene outweigh its benefits for pain relief at recommended doses.

In July 2009, FDA announced an ongoing **safety review (http://wayback.archive-it.org/7993/20161024032946/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm170769.htm)** of propoxyphene, which included evaluating its potential effects on the heart.

Additional Information for Patients

If you currently take propoxyphene-containing products, you should:

- Talk to your healthcare professional about discontinuing propoxyphene and switching to alternative pain medicines.
- Talk to your healthcare professional if you have any concerns about propoxyphene.
- Contact your healthcare professional right away if you experience an abnormal heart rate or rhythm or other symptoms including dizziness, lightheadedness, fainting or heart palpitations.
- Report any side effects with propoxyphene to FDA's MedWatch program using the information at the bottom of the page in the "Contact Us" box.

Dispose of unused propoxyphene in your household trash by following the recommendations outlined in the Federal Drug Disposal Guidelines:

- Take your propoxyphene out of its original container and mix it with an undesirable substance, such as used coffee grounds or kitty litter. The medication will be less appealing to children and pets, and unrecognizable to people who may intentionally go through your trash.
- Put the medication in a sealable bag, empty can, or other container to prevent it from breaking out of a garbage bag.

Additional Information for Healthcare Professionals

FDA recommends that healthcare professionals:

- Stop prescribing and dispensing propoxyphene-containing products to patients.
- Contact patients currently taking propoxyphene-containing products and ask them to discontinue the drug.
- Inform patients of the risks associated with propoxyphene.
- Discuss alternative pain management strategies other than propoxyphene with your patients.
- Be aware of the possible risk of cardiac conduction abnormalities (prolonged QT, PR, and QRS intervals) in patients taking propoxyphene and assess patients for these events if they present with any signs or symptoms of arrhythmia.
- Report any side effects with propoxyphene to FDA's MedWatch program using the information at the bottom of the page in the "Contact Us" box.

Data Summary

Following receipt of a Citizen Petition requesting the withdrawal of propoxyphene-containing products from the United States market, FDA convened an Advisory Committee meeting on January 30, 2009. After presentations by FDA, the petitioner, and the company reviewing the efficacy and safety data from the propoxyphene drug applications, the literature and postmarketing safety databases, the committee voted by a narrow margin (14-to-12) against the continued marketing of propoxyphene products. Those who voted for propoxyphene to remain on the market advised requiring improved labeling, particularly with warnings about use in elderly patients and about use with concomitant opioids or alcohol. Finally, there was general agreement that additional information about the cardiac effects of propoxyphene would be relevant in further weighing the risk and benefit. As a result, under new authorities given to FDA by the Food and Drug Administration Amendments Act (FDAAA), the agency required the drug manufacturer to conduct a thorough QT study to formally evaluate the effects of propoxyphene on cardiac electrophysiology. In order to determine a safe supratherapeutic dose to incorporate into the Thorough QT study, FDA required the drug manufacturer to first conduct a multiple-ascending dose (MAD) study.

The MAD study was a randomized, double-blind, placebo-controlled sequential multiple-ascending dose study of propoxyphene for 11 days. The study was conducted in healthy volunteers. The first cohort of study subjects was dosed with a total daily dose of 600 mg of propoxyphene (the maximum labeled dose) and the second cohort was dosed with a total daily dose of 900 mg. Additional doses were planned, however the study was placed on clinical hold due to safety concerns. Study subjects were monitored with telemetry and intermittent ECG recordings, comparable to the monitoring that would occur during a Thorough QT study. The drug manufacturer has submitted to FDA the results from the 600 mg and 900 mg cohorts.

Significant QTc interval prolongations were observed with the propoxyphene 600 mg and 900 mg dose levels. With the 600 mg daily dose, at steady state on Treatment Day 11, the largest mean change of QTcF* ($\Delta\Delta$QTcF) was 29.8 milliseconds (ms), which occurred 7 hours after the last dose; with the 900 mg dose the largest mean change was 38.2 ms, which occurred 2 hours after the last dose. It is recognized in the International Conference on Harmonisation (ICH) E14 Guideline1 that drugs that prolong the mean QT/QTc interval by >20 ms have a substantially increased likelihood of being proarrhythmic. In addition, a dose-dependent prolongation of PR and QRS intervals was observed in the study.

Because the elderly and patients with renal insufficiency have a reduction in the clearance of propoxyphene and its cardioactive metabolite, norpropoxyphene, through the kidneys, these populations can be especially susceptible to proarrhythmic effects of the drug.

FDA has concluded that the safety risks of propoxyphene outweigh its limited benefits2-6 for pain relief at recommended doses.

**QTcF is the QT interval corrected for heart rate using the Fridericia formula (cubic root – QTcF = QT/RR1/3).*

References

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Contact FDA

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