



December 5, 2008

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Legacy ID No. 2006P-0090, Docket No. 2006-P-0270, Immediately begin the phased removal from the market of propoxyphene (Darvon) and all propoxyphene-containing products such as Darvocet (propoxyphene and acetaminophen).

Dear Sir/Madam:

The American Society of Health-System Pharmacists (ASHP) is pleased to submit written comments pertaining to the petition to remove propoxyphene and propoxyphene-containing products from the United States drug market. For more than 60 years, ASHP has helped pharmacists who practice in hospitals and health systems improve medication use and enhance patient safety. The Society's 35,000 members include pharmacists and pharmacy technicians who practice in inpatient, outpatient, home-care, and long-term-care settings, as well as pharmacy students.

ASHP policy advocates that the Food and Drug Administration (FDA) withdraw propoxyphene from the United States market based on the drug's poor effectiveness and safety profiles, and because more effective and safer alternatives are available to treat mild to moderate pain.¹ The Society provides the following information to support its recommendation.

Effectiveness

Propoxyphene has been used for treatment of mild to moderate pain, but it is inadequate for managing severe pain.² A meta-analysis of 26 randomized, controlled studies of 2231 patients with postoperative, arthritis, or musculoskeletal pain that compared the effectiveness of acetaminophen plus propoxyphene with that of acetaminophen alone, or placebo, demonstrated that the addition of propoxyphene napsylate 100 mg to patients' pain regimen was no more effective than using acetaminophen alone.³ Similarly, an

evaluation of patients with moderate to severe post-operative pain found that propoxyphene–acetaminophen combination therapy had only similar effectiveness compared to tramadol 100 mg, but was less effective than ibuprofen 400 mg at controlling pain for four to six hours.^{4,5}

Safety

The most common adverse effects from propoxyphene at the recommended dosage are dizziness, sedation, nausea, and vomiting.² While less than 1% of patients taking the recommended dosage of propoxyphene experience adverse effects,⁶ some patient populations, such as the elderly and those with kidney and liver disease, are at greater risk.²

Studies have demonstrated that propoxyphene is commonly prescribed for elderly patients, especially those living in nursing homes. An assessment of prescribing practices for 21,380 nursing homes residents with persistent pain found that propoxyphene was prescribed for 18% of patients.⁷ It should be noted that propoxyphene is not recommended for treatment of chronic pain. Extended use of the drug places this already vulnerable patient population at greater risk of harm.

Propoxyphene has been listed among drugs and drug classes defined by the Beers Criteria⁸ and Zhan Criteria as potentially inappropriate medication for older adults, since the drug offers few advantages over acetaminophen while causing the adverse effects associated with opiate analgesics. Elderly patients taking propoxyphene who experience central nervous system effects may be prone to falls that result in bone fractures, including hip fractures, that can lead to significant morbidity and mortality. Based on the Beers criteria, the National Committee on Quality Assurance included propoxyphene in a list of medications to avoid in the elderly in the 2006 Health Plan Employer Data and Information Set. The avoidance of propoxyphene has also been recommended by the Agency for Healthcare Research and Quality, the Veterans Health Administration, and other health systems as a strategy to improve patient care.^{9,10,11,12}

Propoxyphene poses a unique concern when it is prescribed for elderly and other patients at risk for intentional or unintentional overdose. The lethal dose of propoxyphene is low (750 mg as the hydrochloride salt or 1150 mg as the napsylate salt) when compared to the therapeutic dose (65 mg as the hydrochloride salt every 4 hours as needed, not to exceed 390 mg/day; the maximum recommended daily dosage of the napsylate salt is 600 mg).² Alcohol or other central nervous system depressants can potentiate the drug's toxicity.² Death from propoxyphene poisoning can result from respiratory depression and cardiotoxicity (i.e., delayed atrioventricular conduction, cardiac arrhythmias, circulatory impairment, and cardiorespiratory arrest).² The drug has been linked to 7109 deaths, including 2110 accidental deaths in the United States between 1981 and 2002.¹³

In summary, ASHP believes that the usefulness of propoxyphene to treat pain is limited, and that the possible risks clearly outweigh any potential benefit. A number of

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alternative analgesic therapies (e.g., acetaminophen, ibuprofen, and tramadol) have demonstrated superior effectiveness and safety for the treatment of mild to moderate pain. Based on this evidence, the Society encourages the complete withdrawal of propoxyphene from the U.S. market.

ASHP appreciates this opportunity to present its written comments pertaining to the petition. Feel free to contact me if you have any questions regarding our comments. I can be reached by telephone at 301-664-8702, or by e-mail at jcoffey@ashp.org.

Sincerely,

A handwritten signature in cursive script that reads "Justine Coffey".

Justine Coffey, JD, LLM
Director, Federal Regulatory Affairs

References

1. ASHP policy 0723. Removal of propoxyphene from the market. Available at <http://www.ashp.org/Import/PRACTICEANDPOLICY/PolicyPositionsGuidelinesBestPractices/BrowsebyDocumentType/PolicyPositions/ASHPPolicyPositionsGovernmentLawandRegulation.aspx#0723> (accessed 2008 Nov 17).
2. McEvoy GK, ed. Propoxyphene hydrochloride/propoxyphene napsylate. In: *AHFS Drug Information 2008*. Bethesda, MD: American Society of Health-System Pharmacists; 2008:2207-8.
3. Li Wan Po A, Zhang WY. Systematic overview of co-proxamol to assess analgesic effects of addition of dextropropoxyphene to paracetamol. *BMJ*. 1997; 315:1565-71.
4. The Oxford League. Table of analgesic efficacy. Available at: <http://www.jr2.ox.ac.uk/bandolier/booth/painpag/Acutrev/Analgesics/lftab.html> (accessed 2008 Oct 8).
5. Collins SL, Edwards JE, Moore RA et al. Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain. *Cochrane Database Syst Rev*. 2000; (2):CD001440.
6. Darvon prescribing information. Newport, KY: Xanodyne Pharmaceuticals, Inc; 2006 Feb.
7. Won AB, Lapane KL, Vallow S et al. Persistent nonmalignant pain and analgesic prescribing patterns in elderly nursing home residents. *J Am Geriatr Soc*. 2004; 52:867-74.
8. Fick DM, Cooper JW, Wade WE et al. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. *Arch Intern Med*. 2003; 163:2716-24.
9. VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel. Review of the efficacy and safety of propoxyphene. March 2006. Available at: <http://www.pbm.va.gov/reviews/Propoxyphene.pdf> (accessed 2008 Oct 8).
10. VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel. Criteria for nonformulary use of propoxyphene. October 2006. Available at: <http://www.pbm.va.gov/criteria/Propoxyphene.pdf> (accessed 2008 Oct 8).
11. Zahn C, Sangle J, Bierman AS et al. Potentially inappropriate medication use in the community-dwelling elderly: Findings from the 1996 Medical Expenditure panel Survey. *JAMA*. 2001; 286:2823-9.
12. Pugh MJV, Fincke BG, Bierman AS et al. Potentially inappropriate prescribing in elderly veterans: Are we using the wrong drug, wrong dose, or wrong duration? *J Am Geriatr Soc*. 2005; 53:1282-9.
13. Public Citizen Health Research Group. Petition to the U.S. Food and Drug Administration. February 28, 2006. Available at: <http://www.citizen.org/publications/release.cfm?ID=7420> (accessed 2008 Oct 8).