

Kansas Foundation for Medical Care, Inc.

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## FDA Takes Action on Propoxyphene Products

### Further Safety Studies Are Needed

The U.S. Food and Drug Administration (FDA) is taking several actions to reduce the risk of overdose in patients using pain medications containing propoxyphene (Darvocet N<sup>®</sup>, Darvon<sup>®</sup> and generic equivalents). The actions were taken because of data linking propoxyphene and intentional and unintentional fatal overdoses.

The agency is requiring manufacturers of propoxyphene-containing products to strengthen the label, including the boxed warning, emphasizing the potential for overdose when using these agents. These manufacturers will also be required to provide a medication guide to patients stressing the importance of using the drugs as directed.

FDA is aware of evidence of fatal overdose, both accidental and intentional, involving propoxyphene. In Europe, there is recent evidence that this medication may be more lethal in overdose situations than other pain medications. FDA is taking action to reduce the likelihood of such fatalities in the United States while they fully investigate the safety of propoxyphene.

#### FDA Stops Short of Removing From Market

Based on all evidence available to the agency, the FDA has concluded that the benefits of propoxyphene for pain relief at recommended doses outweigh the safety risks at this time. Therefore, the FDA is not proposing removal of propoxyphene products from the U.S. market.

FDA recognizes that there are unanswered questions about the safety of propoxyphene when used at doses higher than recommended in the official labeling. These unanswered questions include pro-arrhythmic effects on the heart in overdose situations caused by the primary metabolite, norpropoxyphene.

Accordingly, the FDA is requiring the manufacturer to conduct a safety study specifically addressing propoxyphene's potential cardiac effects. In addition, FDA plans to work with other Federal agencies (e.g., Centers for Medicare and Medicaid Services (CMS), Department of Veterans Affairs (VA)) to conduct additional studies regarding the safety of products that contain propoxyphene as compared to other commonly used pain medications.

The following studies are in the planning stages or under discussion:

- FDA is working with CMS to study the safety and prescribing patterns of propoxyphene among the elderly. Specifically, FDA will examine the rates of fatalities and hip fractures among elderly patients taking propoxyphene-acetaminophen and compare these rates to those in elderly persons taking other analgesics.
- FDA will discuss a study examining the safety of propoxyphene-acetaminophen with the Veterans Administration, using the VA's databases.
- FDA is planning to examine the feasibility of studying the safety of propoxyphene with one or more of its epidemiology contractors (Vanderbilt University, Kaiser-California, the HMO Research Network at Harvard Pilgrim Health, and Ingenix).
- FDA will examine the possibility of reviewing Medical Examiner data in the Substance Abuse and Mental Health Administration's (SAMSHA) Drug Abuse Warning Network (DAWN).

The actions of the FDA were taken in response to a petition filed in February 2006 by the public interest group Public Citizen. The petition requested removal of propoxyphene products from the market on grounds that these products have a low margin of safety and have been shown to be less effective than other products with the same indication.

There is a growing list of concerns associated with the use of propoxyphene products. Among older adults, these products constitute an independent risk factor for hip fractures and are poorly tolerated.<sup>1</sup> In addition, older adults are at risk for accumulation of inactive metabolites which may induce opioid-type adverse effects.<sup>1</sup> Coupled with studies demonstrating no superiority over acetaminophen for pain, the relative risk-benefit of these products is highly questionable. Two FDA committees (Anesthetic and Life Support Drugs and the Drug Safety and Risk Management Advisory Committee) concluded that there is still insufficient data to warrant propoxyphene's withdrawal, further work is needed to assess safety.

1. Kamal-Bahl SJ, et al. Propoxyphene use by community-dwelling and institutionalized elderly medicare beneficiaries. *J Am Geri Soc* 2003;41:1099-1104.

## Warfarin-NSAID Therapy and Risk for GI Bleeding

The number of medications that interact with warfarin resulting in changes in its activity are numerous and represent the most common medication category associated with preventable adverse drug events occurring in older adults in the ambulatory setting.<sup>1</sup> It is generally well known that concomitant use of nonsteroidal anti-inflammatory drugs (NSAID) increase the risk that patients may develop a GI bleeding episode as a result of this combination. However, not all NSAIDs carry the same risk.

NSAIDs cause dose and duration-dependent GI erosions in a substantial proportion of patients.<sup>2</sup> Most of these erosions are asymptomatic, but the risk of hemorrhage is heightened considerably by the use of warfarin, even in patients whose INR lies within the desired range. COX-2 inhibitors, celecoxib (Celebrex<sup>®</sup>), possess a couple of advantages over non-selective NSAIDs. First, at therapeutic doses COX-2 inhibitors have no effect on platelet aggregation and bleeding time. Second, they may cause fewer GI ulcers than non-selective NSAIDs.

Several observational studies have investigated the impact of concurrent use of warfarin with either traditional NSAID (tNSAID) and/or COX-2 inhibitors on the incidence of GI bleeding episodes. The largest study (N=35,548) identified was a retrospective cohort of patients in a large nonprofit health maintenance organization.<sup>3</sup> In this study, the rates of hospitalization for GI bleeding events were analyzed in 3 groups, those taking warfarin alone, warfarin plus a tNSAID and warfarin plus a COX-2 inhibitor. The adjusted hazard ratio (HR) for GI bleeding events resulting in an acute hospitalization were:

Agents	HR
Warfarin + tNSAID vs. warfarin alone (95% CI 2.31 to 5.55; p < 0.01)	3.58
Warfarin + COX-2 vs. warfarin alone (95% CI 0.60 to 4.84; p = 31)	1.71
Warfarin + tNSAID vs. warfarin + COX-2 (95% CI 1.42 to 9.60; p < 0.01)	3.69

The rate of GI bleeding in the warfarin plus tNSAID study population was 47.9 events per 1000 patient-years versus 12.1 events per 1000 patient-years in the warfarin plus COX-2 inhibitor. Concurrent use of warfarin plus a COX-2 inhibitor was limited however (N=1601) resulting in insufficient statistical power to detect an increase in bleeding rates within this population.

Another study based on data from the Ontario Drug Benefit Program investigated the risks associated with concomitant use of NSAID and COX-2 inhibitors with warfarin. The outcome was hospitalizations for UGI hemorrhage.<sup>4</sup> Among 98,821 elderly patients

continuously taking warfarin, there were 361 (0.3%) admitted to the hospital with UGI hemorrhage. After adjusting for confounders, the findings of this study suggest that increases in the risk of UGI hemorrhage (odds ratio) are similar between warfarin users concomitantly taking either tNSAIDs or COX-2 inhibitors.

Agent	Odds Ratio	95% Confidence Interval
NSAID	1.9	1.4 to 3.7
Celecoxib	1.7	1.2 to 3.6
Rofecoxib*	2.6	1.7 to 3.6

\*no longer available in the US

The rate GI bleeding (0.3%) was surprisingly low compared to rates of 1-7% reported in the older population.<sup>5</sup> This low rate was considered secondary to intermittent dosing of anti-inflammatory agents and other patient-level factors.

In considering this evidence, one must remember that these were observational studies. The decisions to use NSAIDs in persons taking warfarin would likely be influenced by unmeasured (confounders) patient-level factors, such as lower risks for UGI events, smoking status, alcohol use, or OTC medications. In addition, short term exposures to NSAIDs for acute events may have different risk patterns than chronic exposure. Despite these limitations, though, it is clear that warfarin has the potential for negative outcomes when combined with NSAIDs.

In Kansas, concomitant warfarin and NSAID exposure is the third most frequent drug-drug interaction identified through Kansas Medicare data. While these interactions may be thought to be “managed” in practice through dose modification and appropriate INR monitoring, these combinations do pose increase risks for adverse outcomes in real world settings. Non-selective antiinflammatory agents (tNSAID) significantly increase the risk for serious UGI bleeding events. Use of COX-2 selective agents decreases but does not totally eliminates the risk for serious bleeding events.

1. Gurwitz JH, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA* 2003;289(9):1107-1116.
2. Fortun PJ, et al. Nonsteroidal anti-inflammatory drugs and the small intestine. *Curr Opin Gastroenterol* 2007;23:134-41.
3. Cheetham TC, et al. Gastrointestinal safety of nonsteroidal anti-inflammatory drugs and selective cyclooxygenase-2 inhibitors in patients on warfarin. *Ann Pharmacother* 2009;43:1765-1773.
4. Battistella M, et al. Risk of upper gastrointestinal hemorrhage in warfarin users treated with nonselective NSAIDs or COX-2 inhibitors. *Arch Intern Med* 2005;165:189-192.
5. Kuijer PM, et al. Prediction of the risk of bleeding during anticoagulant treatment for venous thromboembolism. *Arch Intern Med*. 1999;159:457-460.