FDA Drug Bulletin

February - March 1979

CHANGE OF ADDRESS: Address changes for those labels marked with a "Q" should be sent to FDA *Drug Bulletin*/HFI-20, Rockville, Md. 20857. If your label is not identified with a "Q" send address changes to the professional association to which you belong, i.e.: American Medical Association, American Osteopathic Association, American Dental Association, American Nurses Association, American Pharmaceutical Association, American Podiatry Association, or the American Student Pharmaceutical Association. FDA *cannot* change any address taken from a professional association mailing list, so check your mailing label before requesting an address change.

Fatalities Due To Propoxyphene

FDA calls to the attention of physicians, dentists, pharmacists, and other health professionals several serious risks associated with the use of propoxyphene (sold as Darvon, Darvon Compound, Darvon-N, Darvocet-N, other brand names, and under the generic name).

Propoxyphene products are widely used prescription analgesics in hospitals, clinics, and out-patient settings. Darvon products are the most frequently prescribed brand name analgesics, with over 30 million prescriptions written in 1978.

The major hazards associated with propoxyphene use are:

- An estimated one to two thousand deaths a year are associated with propoxyphene alone or in combination with other drugs, FDA estimates. The majority of these appear to be suicides. Propoxyphene ranks second only to the barbiturates as the leading prescription drug associated with drug fatalities.
- The possibility of accidental death associated with propoxyphene has been recognized more recently and is of growing concern (see *FDA Drug Bulletin*, March-April 1978). Some of these deaths have occurred among drug abusers using propoxyphene in high doses with other drugs or alcohol to get a "high." Other deaths, however, appear to have occurred among people who are not habitual drug abusers and who apparently took propoxyphene in conjunction with tranquilizers, alcohol, or sedatives without understanding the danger.
- There is increasing concern that some of these accidental deaths with multiple drugs may have occurred at propoxyphene doses only slightly higher than the upper limits of the recommended dose.
- Propoxyphene, when taken for an extended period of time, produces physical and psychological dependence of the morphine type. This may occur with as little as 500 to 800 mg. per day of the propoxyphene hydrochloride or 800 to 1200 mg. per day of the napsylate salt of propoxyphene (or about 8 to 12 tablets/capsules per day). Because of this dependence liability, propoxyphene was placed in Schedule IV of the Controlled Substances Act in 1977.

The usual cause of death associated with propoxyphene overdosage appears to be respiratory depression, a typical action of narcotics. Some researchers have suggested that cardiac toxicity due to norpropoxyphene, the major metabolite, may also be a factor in some propoxyphene-related deaths, but this is not known to be a frequent mechanism in accidental deaths.

FDA is now reevaluating all propoxyphene products, including propoxyphene HCl, propoxyphene napsylate, and combinations of these with aspirin, acetaminophen, and APC. The purpose of the reevaluation is to determine whether there is a need for additional warnings in the labeling, for a change in the scheduling of the drug under the Controlled Substances Act, or for withdrawal of the drug from the market.

An additional issue to be addressed during the reevaluation is the effectiveness of propoxyphene. Propoxyphene is prescribed most often (about 80 percent of the time) in combinations also containing aspirin, acetaminophen, or APC. Several new studies suggest that the contribution to overall effectiveness of the propoxyphene component in these combinations is minimal. As a single ingredient, propoxyphene in doses of 32 mg to 65 mg is approximately two-thirds as potent as codeine and is no more effective—and may be less effective—than the usual doses of aspirin or acetaminophen.

One part of the FDA reevaluation of propoxyphene will be an open hearing on April 6 at which health professionals and other interested persons can present their views. The hearing will seek additional information on the effectiveness and risks of propoxyphene. Future issues of the *Drug Bulletin* will report on FDA's reevaluation.

Health professionals can do much to reduce the number of fatalities associated with propoxyphene.

- Doctors and dentists are advised before prescribing propoxyphene to consider whether the patient may be suicidal, abuse prone, or addiction prone.
- Health professionals are advised to discuss with patients the abuse potential of propoxyphene and the possibility of its being dangerous if taken with alcohol, tranquilizers, or sedatives.
- Pharmacists are advised to warn people orally and on prescription drug labels not to take propoxyphene drugs with alcohol, tranquilizers, or sedative-hypnotics.

Update on Estrogens and Uterine Cancer

FDA has reviewed three recent studies on estrogen use, and the Agency concludes the new research affirms that menopausal and postmenopausal women who take estrogens have an increased risk of endometrial cancer. Although one of the studies[1] criticizes research linking estrogen therapy and cancer on methodological grounds, others[3,4] have attempted to address the objections.

The new data also strongly support estrogen label