



0537 '00 FEB 23 9:34
FAX

To: Mr. Greg Davis
Company: FDA

From: Alan T. Roberts

Subject: Docket 99P-4649/CP 1
Date: 1/27/00 **# of Pages Transmitted:** 4

Dear Greg:

Enclosed in this fax please find the revised pages that deal specifically with the **DOSAGE AND ADMINISTRATION** section of the petition.

Since the maximum recommended dosage of the acetaminophen comes into play with the proposed drug product more so than the maximum recommended dosage of the propoxyphene napsylate, I have revised the wording of the proposed insert to read, "Not to exceed 8 tablets/capsules in 24 hours." The affected pages are as follows:

- 1) The fourth page of the proposed insert (Attachment B),
- 2) The fourth page of the side-by-side comparison (Attachment C), and
- 3) The tenth page of Attachment C (first page of explanation of differences).

I am only faxing and express mailing the revised pages. Should Mikart need to submit complete, revised attachments, please contact me.

I trust this information is satisfactory. Thank you for your phone call, and for your attention to this matter.

Sincerely,

Alan T. Roberts
Director of Research and Development

Attachments

99P-4649

CRI

Drug Interactions

The CNS-depressant effect of propoxyphene is additive with that of other CNS depressants, including alcohol. As in the case with many medicinal agents, propoxyphene may slow the metabolism of a concomitantly administered drug. Should this occur, the higher serum concentrations of that drug may result in increased pharmacologic or adverse effects of that drug. Such occurrences have been reported when propoxyphene was administered to patients on antidepressants, anticonvulsants, or warfarin-like drugs. Severe neurologic signs, including coma, have occurred with concurrent use of carbamazepine.

Usage in Pregnancy

Safe use of propoxyphene in pregnancy has not been established relative to possible adverse effects on fetal development. Instances of withdrawal symptoms in the neonate have been reported following usage during pregnancy. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Nursing Mothers

Low levels of propoxyphene have been detected in human milk. In postpartum studies involving nursing mothers who were given propoxyphene, no adverse effects were noted in infants receiving mother's milk.

Usage in Pediatric Patients

Safety and effectiveness in pediatric patients have not been established.

Usage in the Elderly

The rate of propoxyphene metabolism may be reduced in some patients. Increase dosing interval should be considered.

A Patient Information Sheet is available for this product. See the text following **HOW SUPPLIED** section below.

ADVERSE REACTIONS

In a survey conducted in hospitalized patients, less than 1% of patients taking propoxyphene at recommended doses experienced side effects. The most frequently reported were dizziness, sedation, nausea, and vomiting. Some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, hallucinations and minor visual disturbances.

Liver dysfunction has been reported in association with both active components of Propoxyphene Napsylate and Acetaminophen Tablets/Capsules. Propoxyphene therapy has been associated with abnormal liver function tests and, more rarely, with instances of reversible jaundice (including cholestatic jaundice). Hepatic necrosis may result from acute overdose of acetaminophen (see Management of Overdosage). In chronic ethanol abusers, this has been reported rarely with short-term use of acetaminophen dosages of 2.5 to 10 g/day. Fatalities have occurred.

Renal papillary necrosis may result chronic acetaminophen use, particularly when the dosage is greater than recommended and when combined with aspirin.

Subacute painful myopathy has occurred following chronic propoxyphene overdose.

DOSAGE AND ADMINISTRATION

This product is given orally. The usual dosage is 50 mg propoxyphene napsylate and 500 mg of acetaminophen every 4 hours as needed for pain; not to exceed 8 tablets/capsules in 24 hours. Consideration should be given to a reduced total daily dosage in patients with renal impairment.

**SIDE BY SIDE INSEKΓ LABELING COMPARISON OF THE REFERENCE DRUG,
DARVO CET N-100, AND PROPOXYPHENE AND ACETAMINOPHEN
TABLETS/CAPSULES USP
(50 MG/500 MG)**

Drug Interactions—The CNS-depressant effect of propoxyphene is additive with that of other CNS depressants, including alcohol.

As is the case with many medicinal agents, propoxyphene may slow the metabolism of a concomitantly administered drug. Should this occur, the higher serum concentrations of that drug may result in increased pharmacologic or adverse effects of that drug. Such occurrences have been reported when propoxyphene was administered to patients on antidepressants, anticonvulsants, or warfarin-like drugs. Severe neurologic signs, including coma, have occurred with concurrent use of carbamazepine.

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Instances of withdrawal symptoms in the neonate have been reported following usage during pregnancy. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Nursing Mothers—Low levels of propoxyphene have been detected in human milk. In postpartum studies involving nursing mothers who were given propoxyphene, no adverse effects were noted in infants receiving mother's milk.

Usage in Pediatric Patients—Safety and effectiveness in pediatric patients have not been established.

Usage in the Elderly—The rate of propoxyphene metabolism may be reduced in some patients. Increased dosing interval should be considered.

A Patient Information Sheet is available for this product. See text following "How Supplied" section below.

ADVERSE REACTIONS

In a survey conducted in hospitalized patients, less than 1% of patients taking propoxyphene hydrochloride at recommended doses experienced side effects. The most frequently reported were dizziness, sedation, nausea, and vomiting. Some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, hallucinations, and minor visual disturbances.

Liver dysfunction has been reported in association with both active components of Darvocet-N 50 and Darvocet-N 100. Propoxyphene therapy has been associated with abnormal liver function tests and, more rarely, with instances of reversible jaundice (including cholestatic jaundice). Hepatic necrosis may result from acute overdose of acetaminophen (see Management of Overdosage). In chronic ethanol abusers, this has been reported rarely with short-term use of acetaminophen dosages of 2.5 to 10 g/day. Fatalities have occurred.

Renal papillary necrosis may result from chronic acetaminophen use, particularly when the dosage is greater than recommended and when combined with aspirin.

Subacute painful myopathy has occurred following chronic propoxyphene overdosage.

DOSAGE AND ADMINISTRATION

These products are given orally. The usual dosage is 100 mg propoxyphene napsylate and 650 mg acetaminophen every 4 hours as needed for pain. The maximum recommended dose of propoxyphene napsylate is 600 mg per day.

Consideration should be given to a reduced total daily dosage in patients with hepatic or renal impairment.

Drug Interactions

The CNS-depressant effect of propoxyphene is additive with that of other CNS depressants, including alcohol. As in the case with many medicinal agents, propoxyphene may slow the metabolism of a concomitantly administered drug. Should this occur, the higher serum concentrations of that drug may result in increased pharmacologic or adverse effects of that drug. Such occurrences have been reported when propoxyphene was administered to patients on antidepressants, anticonvulsants, or warfarin-like drugs. Severe neurologic signs, including coma, have occurred with concurrent use of carbamazepine.

Usage in Pregnancy

Safe use of propoxyphene in pregnancy has not been established relative to possible adverse effects on fetal development. Instances of withdrawal symptoms in the neonate have been reported following usage during pregnancy. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Nursing Mothers

Low levels of propoxyphene have been detected in human milk. In postpartum studies involving nursing mothers who were given propoxyphene, no adverse effects were noted in infants receiving mother's milk.

Usage in Pediatric Patients

Safety and effectiveness in pediatric patients have not been established.

Usage in the Elderly

The rate of propoxyphene metabolism may be reduced in some patients. Increase dosing interval should be considered.

A Patient Information Sheet is available for this product. See the text following HOW SUPPLIED section below.

ADVERSE REACTIONS

In a survey conducted in hospitalized patients, less than 1% of patients taking propoxyphene at recommended doses experienced side effects. The most frequently reported were dizziness, sedation, nausea, and vomiting. Some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, hallucinations and minor visual disturbances.

Liver dysfunction has been reported in association with both active components of Propoxyphene Napsylate and Acetaminophen Tablets/Capsules. Propoxyphene therapy has been associated with abnormal liver function tests and, more rarely, with instances of reversible jaundice (including cholestatic jaundice). Hepatic necrosis may result from acute overdose of acetaminophen (see Management of Overdosage). In chronic ethanol abusers, this has been reported rarely with short-term use of acetaminophen dosages of 2.5 to 10 g/day. Fatalities have occurred.

Renal papillary necrosis may result chronic acetaminophen use, particularly when the dosage is greater than recommended and when combined with aspirin.

Subacute painful myopathy has occurred following chronic propoxyphene overdosage.

DOSAGE AND ADMINISTRATION

This product is given orally. The usual dosage is 50 mg propoxyphene napsylate and 500 mg of acetaminophen every 4 hours as needed for pain; not to exceed 8 tablets/capsules in 24 hours. Consideration should be given to a reduced total daily dosage in patients with renal impairment.

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Differences between the proposed Mikart labeling for Propoxyphene Napsylate and Acetaminophen Tablets/Capsules USP (50 mg/500 mg) and the approved insert labeling for the reference listed drug, Darvocet-N (100 mg/650 mg), manufactured by Eli Lilly and Company.

1. The reference listed drug insert is bar coded, while the proposed insert is not.
2. The reference listed drug states “PV 1517 AMP” at the beginning and at the end of the insert. Mikart’s proposed insert has a “Code 000000” at the beginning and at the end of the proposed insert.
3. The reference listed drug also states “Literature revised November 11, 1997”. The proposed insert states “Rev.10/99”
4. The product name for the proposed drug product is **Propoxyphene Napsylate and Acetaminophen Tablets/Capsules USP (50 mg/500 mg)**. The reference listed drug name is **Darvocet-N 50** and **Darvocet-N 100**.
5. The reference listed drug insert addresses the mg and μmol dosage amounts for both active ingredients in the **Darvocet-N 50** and **Darvocet-N 100**. The proposed insert does not.
6. The proposed Mikart insert label contains the statement “**Rx only**” as required by the FDA Modernization Act of 1997. The reference listed drug insert does not contain this statement.
7. The proposed insert has the description, structure, chemical formula, and molecular weight of acetaminophen. The reference listed drug insert does not contain these items.
8. Under **ACTIONS**, the reference listed drug insert reads “Darvocet-N 50 and Darvocet-N 100 provide the analgesic activity. . .” whereas, the proposed insert reads “Propoxyphene Napsylate and Acetaminophen Tablets/Capsules provide the analgesic activity. . .”
9. Under **INDICATIONS**, the reference listed drug states “These products. . .” whereas the proposed insert states “This product. . .”
10. Under **DOSAGE AND ADMINISTRATION**, the reference listed drug states “These products. . .” whereas the proposed insert states “This product. . .” Also, the reference listed drug states “The maximum recommended dose of propoxyphene napsylate is 600 mg per day.” The proposed insert states “. . .not to exceed 8 tablets/capsules in 24 hours.”
11. The dosage of acetaminophen is 650 mg in the reference listed drug, Darvocet-N 100. The dosage of acetaminophen in the proposed product is 500 mg.
12. The reference listed drug refers to **Darvon**. The proposed insert has replaced the word “Darvon” with “Propoxyphene”.



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FORM 700-010, REV. 11/96 SUPERSEDES: REV. 05/95