PRODUCT MONOGRAPH

DARVON-N®

propoxyphene napsylate

100 mg capsules

Analgesic

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PRODUCT MONOGRAPH

DARVON-N

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100 mg capsules

PHARMACOLOGICAL CLASSIFICATION

Analgesic

ACTION

Propoxyphene is a centrally acting, mild narcotic analgesic agent structurally related to methadone.

Equimolar doses of propoxyphene napsylate or propoxyphene hydrochloride provide similar plasma concentrations. Following administration of 100, 200 or 300 mg of propoxyphene napsylate, the bioavailability of propoxyphene is equivalent to that of 65, 130 or 195 mg of propoxyphene hydrochloride. Peak plasma concentrations of propoxyphene are reached in 2 to 2 1/2 hours. After a 100 mg oral dose of propoxyphene napsylate, peak plasma levels of 0.05 to 0.1 mg/mL are achieved. The napsylate salt tends to be absorbed more slowly than the hydrochloride. At or near therapeutic doses, this difference is small when compared with that among subjects and among doses, but the absorption rate of very large doses of the napsylate salt is significantly lower than that of the equimolar doses of the hydrochloride.

Repeated doses of propoxyphene at 6-hour intervals lead to increase in plasma concentrations, with a plateau after the ninth dose at 48 hours. Propoxyphene is metabolized in the liver to norpropoxyphene. Propoxyphene has a half-life of 6 to 12 hours, whereas that of norpropoxyphene is 30 to 36 hours. Norpropoxyphene has substantially less central nervous system depressant effect than propoxyphene but a greater local anesthetic effect, which is similar to that of amitriptyline and antiarrhythmic agents, such as lidocaine and quinidine. In animal studies in which propoxyphene and norpropoxyphene are continuously infused in large amounts, intracardiac conduction time (PR and QRS intervals) was prolonged. Any intracardiac conduction delay attributable to high concentrations of norpropoxyphene may be of relatively long duration.

INDICATIONS AND CLINICAL USES

Darvon-N is indicated for the relief of mild to moderate pain.

CONTRAINDICATIONS

Darvon-N is contraindicated in persons who have shown hypersensitivity to it.

WARNINGS

DO NOT PRESCRIBE PROPOXYPHENE FOR PATIENTS WHO ARE SUICIDAL OR ADDICTION-PRONE.

PRESCRIBE PROPOXYPHENE WITH CAUTION FOR PATIENTS TAKING TRANQUILIZERS OR ANTI-DEPRESSANT DRUGS AND PATIENTS WHO USE ALCOHOL IN EXCESS.

TELL YOUR PATIENTS NOT TO EXCEED THE RECOMMENDED DOSE AND TO LIMIT THEIR INTAKE OF ALCOHOL.

Propoxyphene products in excessive doses, either alone or in combination with other CNS depressants, including alcohol, are a major cause of drug-related deaths. Fatalities within the first hour of overdosage are not uncommon.

Propoxyphene should not be taken in doses higher than those recommended. The judicious prescribing of propoxyphene is essential to the safe use of this drug. With patients who are depressed or suicidal, consideration should be given to the use of non-narcotic analgesics. Patients should be cautioned about the concomitant use of propoxyphene products and alcohol because of potentially serious CNS-additive effects of these agents. Because of its added depressant effects, propoxyphene should be prescribed with caution for those patients whose medical condition requires the concomitant administration of sedatives, tranquilizers, muscle relaxants, antidepressants, or other CNS-depressant drugs. Patients should be advised of the additive depressant effects of these combinations.

Many of the propoxyphene-related deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts, as well as histories of misuse of tranquilizers, alcohol, and other CNS-active drugs. Some deaths have occurred as a consequence of the accidental ingestion of excessive quantities of propoxyphene alone or in combination with other drugs.

Drug Dependence:

Propoxyphene, when taken in higher-than-recommended doses over long periods of time, can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients:

Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

PRECAUTIONS

Drug Interactions:

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

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 post-partum studies involving nursing mothers who were given propoxyphene, no adverse effects were noted in infants receiving mother's milk.

Usage in Children:

Propoxyphene is not recommended for use in children, because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitant with orphenadrine.

ADVERSE REACTIONS

Such side effects as dizziness, headache, sedation, somnolence, paradoxical excitement, insomnia, skin rash, and gastrointestinal disturbances (including nausea, vomiting, abdominal pain and constipation) may occur with the recommended doses of Darvon-N. Euphoria, dysphoria and minor visual disturbances also have been reported.

The chronic ingestion of propoxyphene in doses exceeding 800 mg per day has caused toxic psychoses and convulsions. A single dose of 1200 mg of propoxyphene napsylate has caused convulsions.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms:

The manifestations of acute overdosage with propoxyphene are similar to those of narcotic overdosage and include respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, initial pupillary constriction followed by dilation as hypoxia increases, and circulatory collapse. In addition to these characteristics typical of narcotic poisoning, focal and generalized convulsions constitute a prominent feature in most cases of severe propoxyphene poisoning, and cardiac arrhythmias and pulmonary edema have occasionally been reported. Apnea, cardiac arrest and death have occurred.

Treatment:

Primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. The narcotic antagonist, naloxone, is a specific antidote against the respiratory depression produced by propoxyphene.

An appropriate dose of one of these antagonists should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation, and the antagonist should be repeated, as necessary, at 20 to 30 minute intervals, until the patient's condition remains satisfactory. The duration of action of the antagonist may be brief. If no response is observed after 10 mg of naloxone have been administered, the diagnosis of propoxyphene toxicity should be questioned. (Nalorphine and levallorphan may be used if naloxone is not available, but these agents are not as satisfactory as naloxone).

Blood gases, pH, and electrolytes should be monitored in order that acidosis and any electrolytic disturbance present may be promptly corrected. Acidosis, hypoxia, and generalized CNS depression predispose to the development of cardiac arrhythmias. Ventricular fibrillation or cardiac arrest may occur and necessitate the full complement of cardiopulmonary resuscitative (CPR) measures. Respiratory acidosis rapidly subsides as ventilation is restored and hypercapnea eliminated, but residual lactic acidosis may require intravenous bicarbonate for prompt correction.

Electrocardiographic monitoring is essential. Prompt correction of hypoxia, acidosis, and electrolytic disturbance (when present) will help prevent these cardiac complications and will increase the effectiveness of agents administered to restore normal cardiac function.

In addition to the use of a narcotic antagonist, the patient may require careful titration with an anticonvulsant to control convulsions. Analeptic drugs (for example, caffeine or amphetamine) should not be used because of their tendency to precipitate convulsions.

General supportive measures, in addition to oxygen, include, when necessary, intravenous fluids, vasopressor-inotropic compounds, and, when infection is likely, anti-infective agents. Gastric lavage may be useful, and activated charcoal can adsorb a significant amount of ingested propoxyphene. Dialysis is of little value in poisoning due to propoxyphene. Efforts should be made to determine whether other agents, such as alcohol, barbiturates, tranquilizers, or other CNS depressants, were also ingested, since these increase CNS depression as well as cause specific toxic effects.

DOSAGE AND ADMINISTRATION

Darvon-N is given orally. The usual adult dosage is one capsule (100 mg) 3 or 4 times daily. The maximal dose should not exceed 600 mg of propoxyphene napsylate per day.

AVAILABILITY

Darvon-N is available in a size 3 gelatin capsule with a pink body and cap. Each capsule contains:

Propoxyphene Napsylate 100 mg

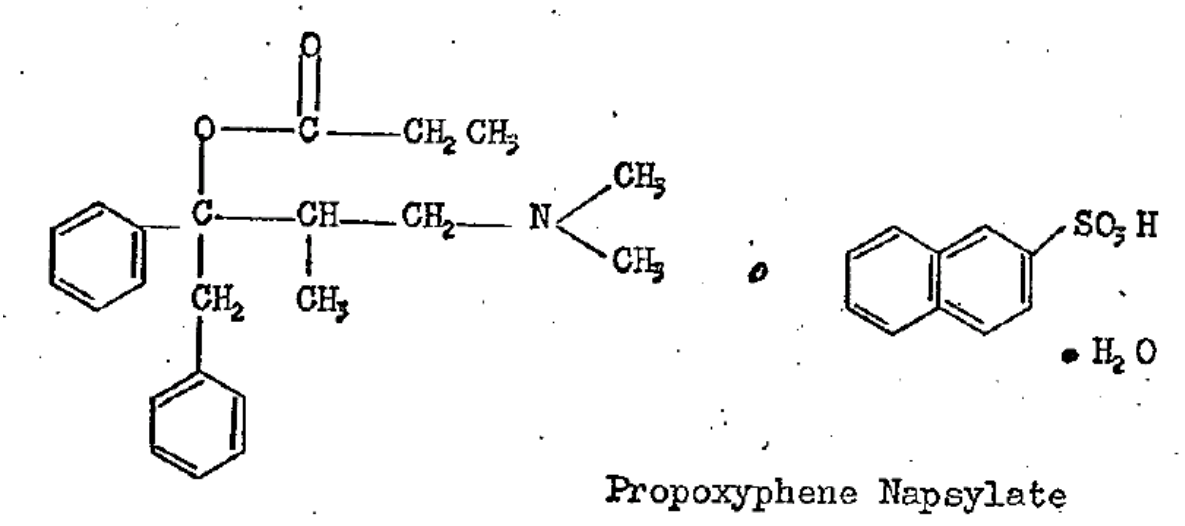
The capsule is imprinted with Paladin and the Identicode H64.

Propoxyphene is included in the Schedule to the Controlled Drugs and Substances Act.

CHEMISTRY

Propoxyphene Napsylate is the 2-naphthalene sulfonic acid salt of propoxyphene. It is dextro-rotatory.

The chemical name of propoxyphene napsylate is: μ-(+)-4(dimethylamino)-3 methyl-1, 2 diphenyl-2-butanol Propionate (ester) 2-Naphthalene-sulfonate (salt) Hydrate with the following molecular structure:



Propoxyphene Napsylate

PHARMACOLOGY

Pharmacologic studies of the effects of d-propoxyphene napsylate have been conducted in laboratory animals. The majority of the studies were comparative with d-propoxyphene hydrochloride.

The studies concerned analgesic, anti-inflammatory, antitussive, and antipyretic effects in rodents, metabolism in rodents, and the effects on vital functions in cats and dogs. Data from these studies support the following conclusions:

1. In subtoxic doses, propoxyphene napsylate is devoid of antipyretic, antitussive, and anti-inflammatory activity.
2. In rats and mice, oral administration of propoxyphene napsylate produces analgesic effects. In the rat, the hydrochloride appears more potent than the napsylate salt. The duration of effect is similar for the two salts. As one increases the availability of d-propoxyphene from the water insoluble napsylate salt the differences in the analgesic potency of the two salts are minimized.
3. Nalorphine antagonizes the analgesic and toxic effects of propoxyphene napsylate.
4. In anesthetized cats, intravenous administration of d-propoxyphene as the napsylate or the hydrochloride decreases respiratory rate and inspiratory volume, and elevates expiratory $\%C0_2$ levels. The changes following d-propoxyphene hydrochloride are generally greater than those seen after d-propoxyphene

napsylate but the differences are not statistically significant. Nalorphine reverses the effects of both d-propoxyphene salts.

5. In unanesthetized dogs, large oral doses of d-propoxyphene as the napsylate or the hydrochloride produce decreases in body temperature and blood pH, and increases in expiratory $\%C0_2$ levels. The maximal effects of the two salts are not significantly different in magnitude or time. In general, rates of recovery of body temperature, blood pH, and expiratory $\%CO_2$ levels are not significantly different for the two salts.

6. In intact rats, orally administered d-propoxyphene napsylate is demethylated in the same manner as d-propoxyphene hydrochloride. Neither d-propoxyphene napsylate nor d-propoxyphene hydrochloride is absorbed from the stomach, however, both are readily absorbed from the small intestine.

7. Therapeutic doses in humans have produced no demonstrable effects on respiration, blood pressure, or reflex activity.

8. Higher plasma levels of propoxyphene have been observed when d-propoxyphene napsylate was given in combination with ASA, than when d-propoxyphene napsylate was given alone.

TOXICOLOGY

The acute lethal doses of the hydrochloride and napsylate salts of propoxyphene were determined in 4 species. The results shown in Figure 1 indicate that, on a molar basis, the napsylate salt is less toxic than the hydrochloride. This may be due to the relative insolubility and retarded absorption of propoxyphene napsylate.

Figure 1

Acute Oral Toxicity of Propoxyphene

Species	LD_{50} (mg/kg ± SE) LD_{50} (mmol/kg) Propoxyphene Hydrochloride	Propoxyphene Napsylate
Mouse	282 + 39 0-75	915 + 163 1.62
Rat	230 + 44 0.61	647 + 95 1.14
Rabbit	ca 82 0.22	>183 >0.32
Dog	ca 100 0.27	>183 >0.32

Propoxyphene napsylate exhibited no effects on the reproductive capacity nor the viability of the young of rats except at doses producing maternal toxicity.

Large doses of propoxyphene napsylate were free of teratogenic effects in rats and rabbits.

The clinical signs of toxicity of propoxyphene napsylate in rats included reduction of growth rate, liver enlargement and slight fatty metamorphosis of the liver. These effects were clearly present in rats given 0.5 and 1.0% drug-diets for extended periods of time. These doses represent approximately 40 to 80 times the human dose. Dietary levels of 0.2% propoxyphene napsylate have been tolerated by rats for 12 months with little, if any, toxicity.

In dogs, repeated daily doses of 40 to 60 mg/kg of propoxyphene napsylate produced loss of body weight, liver enlargement, elevation of serum alkaline phosphatase levels and slight fatty metamorphosis of the liver. Daily doses of 80 mg/kg produced acute intoxication and death in one dog after 23 days of treatment. The signs of clinical toxicity are clearly related to the dose level. Dogs were able to tolerate daily doses of 10 or 20 mg/kg with no apparent toxicity.

It should be emphasized that the effects described above can be induced to the same extent with equimolar doses of d-propoxyphene HCl. It may be anticipated from animal toxicology that the toxicity of d-propoxyphene napsylate in man will be no greater than that produced by d-propoxyphene HCl when repeated doses are given and that the napsylate salt may be less toxic on an acute basis.

INFORMATION FOR THE CONSUMER

Your prescription is for a Darvon-N (propoxyphene napsylate) Product.

Darvon-N is used for the relief of pain.

Although Darvon-N is safe and effective when taken as directed, it is important that you read and understand the information in this leaflet. If you have any questions, ask your doctor or pharmacist.

GENERAL CAUTION

Other Drugs:

Make sure your doctor knows if you are taking tranquilizers, sleep aids, antidepressant drugs, antihistamines or any other drugs that make you sleepy. The use of these drugs with Darvon-N increases their sedative effects and may lead to overdosage symptoms. (See Overdosage below.)

Alcohol:

Heavy use of alcohol with Darvon-N is hazardous and may lead to overdosage symptoms (See Overdosage below). THEREFORE, THE WISEST COURSE IS TO REFRAIN ENTIRELY FROM CONSUMING ALCOHOLS WHILE TAKING DARVON-N.

Regular Activities:

Darvon-N may cause drowsiness or impair your mental and/or physical abilities; therefore, use caution when driving a vehicle or operating dangerous machinery. DO NOT perform any hazardous task unless you are sure there is no reduction in alertness.

Pregnancy:

Do not take a Darvon-N product during pregnancy unless your doctor knows you are pregnant and specifically recommends its use.

Children:

Darvon-N is not recommended for use in children under 12 years of age.

Allergy:

Do not take Darvon-N if you have had an allergic reaction to any dosage form of this drug.

Dependence:

Darvon-N when taken in higher-than-recommended doses over a long period of time, has produced physical and psychological dependence (a craving for the drug or an inability to function normally without the drug).

SIDE EFFECTS

When Darvon-N is taken as directed, side effects are infrequent. Among those reported are drowsiness, dizziness, nausea and vomiting. If these effects do occur, lying down may help.

Less frequently reported side effects include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, minor visual disturbances and feelings of elation or discomfort.

If any one or more of these side effects occur, contact your if physician.

DOSAGE

Your prescription should be taken exactly as directed by your doctor. Do not exceed the maximal daily dose. Always follow dosage recommendations carefully - do not increase the dosage without your doctor's approval. If you miss a dose of the drug, do not take twice as much the next time, but you can take the next normal dose earlier.

OVERDOSAGE

An overdosage of Darvon-N, alone or in combination with other drugs, including alcohol, may cause weakness, difficulty in breathing, confusion, anxiety, and even a severe degree of drowsiness and dizziness. Extreme overdosage can lead to unconsciousness and death.

In any suspected overdosage situation, GET SKILLED EMERGENCY HELP IMMEDIATELY.

Other Information:

This medication was prescribed specifically for you. It should not be given to anyone else even if his/her condition appears to be similar to yours. If you want more information or have any questions about Darvon-N, ask your doctor or pharmacist.

Keep this and all drugs out of the reach of children.