PRODUCT INFORMATION
DOLOXENE®
dextropropoxyphene napsylate)

NAME OF THE MEDICINE

DOLOXENE® (dextropropoxyphene napsylate).

WARNING: The Administrative Appeals Tribunal is expected to hear an appeal in relation to the continued registration of this product towards the end of May 2012. If the appeal against cancellation is rejected, this product may then cease to be available within a short timeframe.

WARNING: For patients currently using dextropropoxyphene-containing products to manage chronic pain who have not recently trialled alternative analgesia, ATTEMPT TO REPLACE dextropropoxyphene-containing products with alternative analgesia before continuing to prescribe dextropropoxyphene-containing products. DO NOT INITIATE the use of dextropropoxyphene-containing products for any NEW PATIENTS, whether for the treatment of acute or chronic pain.

WARNING: Dextropropoxyphene products have recently been associated with substantial prolongation of the QT interval. DOLOXENE is contraindicated in patients with congenital long QT syndrome or known acquired QT interval prolongation. DOLOXENE is also contraindicated in patients with a history of clinically significant cardiovascular disease, congestive heart failure, cardiac hypertrophy, arrhythmia or bradycardia as they are at higher risk of developing Torsade de Pointes, a rare type of ventricular tachycardia. (For other contraindications, see main text.) Elderly patients, and those with renal insufficiency, are also believed to be at higher risk as they are likely to exhibit higher blood levels of dextropropoxyphene and norpropoxyphene. It is STRONGLY RECOMMENDED that all patients undergoing chronic treatment with dextropropoxyphene products have a renal function blood test and an ECG performed at baseline and periodically (at least every 3 months) to monitor for increased risk. Should patients demonstrate significant renal insufficiency (creatinine clearance below 40 mL/min) and/or ECG results of concern, DOLOXENE MUST be ceased immediately.

Dextropropoxyphene napsylate has the following chemical structure:

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\text{\includegraphics{chemical_structure.png}}
\]
Chemically, it is (+)-(1S,2R)-1-benzyl-3-dimethylamino-2-methyl-1-phenylpropyl propionate naphthalene-2-sulphonate monohydrate and its molecular formula is \( \text{C}_{22}\text{H}_{29}\text{NO}_2\text{C}_{10}\text{H}_8\text{O}_3\text{SH}_2\text{O} \). It has a molecular weight of 565.7. The CAS number for dextropropoxyphene napsylate is 26570-10-5.

DESCRIPTION

DOLOXENE (dextropropoxyphene napsylate) is a synthetic, odourless, white crystalline solid with a bitter taste. It is very slightly soluble in water and soluble in methanol, ethanol, chloroform and acetone.

Dextropropoxyphene napsylate differs from dextropropoxyphene hydrochloride in that it allows the formulation of more stable preparations. Because of differences in molecular weight, a dose of 100 mg of dextropropoxyphene napsylate is required to supply an amount of dextropropoxyphene equivalent to that present in 65 mg of dextropropoxyphene hydrochloride.

Each DOLOXENE capsule contains 100 mg dextropropoxyphene napsylate. DOLOXENE also contains the inactive ingredients: starch - pregelatinised maize, dimethicone 350, gelatin, red iron oxide and titanium dioxide.

Dextropropoxyphene napsylate is a centrally acting, synthetic opioid analgesic structurally related to methadone. It binds to opioid receptors at many sites within the central nervous system affecting processes for both the physiological perception of pain and the emotional response to pain. There are multiple subtypes of central and peripheral opioid receptors each mediating therapeutic and/or adverse effects of opioid drugs. The potency of dextropropoxyphene napsylate is from two thirds to equal that of codeine.

Pharmacokinetics

Equimolar doses of dextropropoxyphene hydrochloride or napsylate provide similar plasma concentrations. Following administration of 65, 130 or 195 mg of dextropropoxyphene hydrochloride, the bioavailability of dextropropoxyphene is equivalent to that of 100, 200 or 300 mg respectively of dextropropoxyphene napsylate. Peak plasma concentrations of dextropropoxyphene are reached in 2 to 2 ½ hours. After a 100 mg oral dose of dextropropoxyphene napsylate, peak plasma levels of 0.05 to 0.1 mcg/mL are achieved. As shown in Figure 1, 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.
Because of this several hundredfold difference in solubility, the absorption rate of very large doses of the napsylate salt is significantly lower than that of equimolar doses of the hydrochloride.

Repeated doses of dextropropoxyphene at six-hour intervals lead to increasing plasma concentrations, with a plateau after the ninth dose at 48 hours.

Dextropropoxyphene is metabolized in the liver to yield norpropoxyphene. Dextropropoxyphene 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 dextropropoxyphene but a greater local anaesthetic effect, which is similar to that of amitriptyline and antiarrhythmic agents, such as lignocaine and quinidine.

In animal studies in which dextropropoxyphene and norpropoxyphene were 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**

For the relief of mild to moderate pain in patients who do not respond adequately to other analgesics.

**CONTRAINdications**

Hypersensitivity to dextropropoxyphene.

Concomitant use of alcohol in patients with abuse potential or a history of alcohol or substance abuse.
Patients with a history of clinically significant cardiovascular disease, congestive heart failure, cardiac hypertrophy, arrhythmia or bradycardia.

Patients with conditions, or using drugs, predisposing to hypokalaemia and/or hypomagnesaemia.

Patients with significant hepatic impairment who are at risk of outlying pharmacokinetic/pharmacodynamic (PK/PD) responses (see Drug Interactions).

Patients with congenital long QT syndrome or known acquired QT interval prolongation.

Patients over 80 years of age.

Patients with significant renal impairment (creatinine clearance below 40 mL/min).

Patients taking concomitant medications known to prolong QT interval (e.g. sotalol, quinidine, haloperidol, thioridazine, amitriptyline, clomipramine, chlorpromazine, erythromycin, methadone, clarithromycin, pimozide, amiodarone) and alcohol.

Concomitant use with drugs that are known to be CYP3A4 inhibitors (see Drug Interactions).

Patients with a history of depression or mental illness.

**WARNINGS**

In addition to the black box warnings:

- DO NOT PRESCRIBE DEXTROPROPOXYPHENE FOR PATIENTS WHO ARE SUICIDAL OR PRONE TO DRUG DEPENDENCY.
- PRESCRIBE DEXTROPROPOXYPHENE WITH CAUTION FOR PATIENTS TAKING TRANQUILLIZERS OR ANTIDEPRESSANT DRUGS AND PATIENTS WHO USE ALCOHOL IN EXCESS.
- TELL YOUR PATIENTS NOT TO EXCEED THE RECOMMENDED DOSE OF DOLOXENE AND TO AVOID ALCOHOL.

Dextropropoxyphene 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. In a survey of deaths due to overdosage conducted in 1975, in approximately 20 percent of the fatal cases, death occurred within the first hour (5 percent occurred within 15 minutes). Dextropropoxyphene should not be taken in doses higher than those recommended by the physician. The judicious prescribing of dextropropoxyphene 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 opioid analgesics. Patients should be cautioned about the concomitant use of dextropropoxyphene products and alcohol because of potentially serious CNS-additive effects of these
agents. Because of its added depressant effects, dextropropoxyphene should be prescribed with caution for those patients whose medical condition requires the concomitant administration of sedatives, tranquillizers, muscle relaxants, antidepressants, or other CNS-depressant drugs. Patients should be advised of the additive depressant effects of these combinations.

Many of the dextropropoxyphene-related deaths have occurred in patients with previous histories of emotional disturbance or suicidal ideation or attempts as well as histories of misuse of tranquilizers, alcohol, and other CNS-active drugs. Caution should be exercised in prescribing unnecessarily large amounts of dextropropoxyphene napsylate for such patients (see “OVERDOSAGE”). Some deaths have occurred as a consequence of the accidental ingestion of excessive quantities of dextropropoxyphene alone or in combination with other drugs. Patients taking dextropropoxyphene should be warned not to exceed the dosage recommended by the physician.

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

**Use in Ambulatory Patients** - Dextropropoxyphene 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**

DOLOXENE should be used with caution in patients with anaemia or with renal or hepatic diseases (see also CONTRAINDICATIONS).

**QT prolongation** - A Multiple Ascending Dose (MAD) study using a product containing dextropropoxyphene napsylate (DPP-n) was conducted in the USA. Eighteen healthy volunteers were given tablets containing DPP-n and a further 6 subjects received placebo. The 600 mg dose of DPP-n used as Dose Level 1 of the MAD study equates to 390 mg of dextropropoxyphene hydrochloride. Concomitant paracetamol was not given in the MAD study and dosing over days 1-2 in the trial was <600 mg.

Incremental dosing of dextropropoxyphene from 600 mg daily (Dose Level 1) through to 900 mg (Dose Level 2), 1200 mg, 1500 mg, 1800 mg, 2100 mg and 2400 mg was originally planned. Levels above 600 mg were intended to mimic expected exposure in elderly patients or those with renal impairment. Two cohorts of study subjects were dosed with a total daily dose of 600 mg and the third cohort was given a total daily dose of 900 mg of dextropropoxyphene. Additional doses
were not administered as the study was placed on clinical hold due to safety concerns.

QTc interval prolongations were observed with the dextropropoxyphene 600 mg and 900 mg dose levels. With the 600 mg daily dose, at steady state on Treatment Day 11, the largest mean change of QTcF (difference between active treatment and placebo) was 29.8 milliseconds (ms) (90% confidence interval, 11.7 to 47.9 ms), which occurred seven hours after the last dose. In the 900 mg dose group, the largest mean change was 38.2 ms (90% confidence interval, 19.0 to 57.4 ms), which occurred two hours after the last dose.

**Elderly patients and patients with renal insufficiency** - Elderly patients and patients with renal insufficiency have reduction in clearance of dextropropoxyphene and its metabolite, norpropoxyphene, through the kidneys. These populations are likely to be susceptible to proarrhythmic effects of the drug.

**Patients undergoing chronic treatment** - It is strongly recommended that all patients undergoing chronic treatment with dextropropoxyphene products have a renal function blood test and an ECG performed at baseline and then periodically (minimum three monthly testing recommended) to monitor for increased risk. Should patients demonstrate significant renal insufficiency (creatinine clearance below 40 mL/min) and/or ECG results of concern, DOLOXENE must be ceased immediately.

Use in Pregnancy (Category C): Opioid analgesics may cause respiratory depression in the newborn infant. Withdrawal symptoms in newborn infants have been reported with prolonged use of this class of drugs. These products should only be used during labour after weighing the needs of the mother against the risk to the foetus.

Safe use in pregnancy has not been established relative to possible adverse effects on foetal development. Therefore, dextropropoxyphene should not be used in pregnant women unless, in the judgement of the physician, the potential benefits outweigh the possible hazards.

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

Use in Children - Dextropropoxyphene is not recommended for use in children, because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the paediatric age group.

Use in the Elderly - The rate of dextropropoxyphene metabolism may be reduced in some patients. Increased dosing interval should be considered.
DRUG INTERACTIONS

General - Dextropropoxyphene may inhibit the hepatic metabolism of concomitantly administered drugs. Should this occur, higher serum concentrations of the concomitantly administered drug may result in increased pharmacological and/or adverse effects of that drug. Such occurrences have been reported when dextropropoxyphene has been administered to patients receiving antidepressants, anticonvulsants or warfarin like drugs.

It is expected that dextropropoxyphene is a CYP3A4 substrate and CYP3A4 inhibitors are likely to increase exposure to dextropropoxyphene.

CNS Depressants including Alcohol - Dextropropoxyphene in combination with alcohol, tranquillisers, sedative-hypnotics and other central nervous system depressants has additive depressant effects and the patient should be so advised. Patients taking DOLOXENE should be warned not to exceed the dosage recommended by their physician (see "WARNINGS").

Warfarin - Concomitant warfarin and dextropropoxyphene administration may increase serum concentrations of warfarin. Warfarin dosage adjustments may be required.

Carbamazepine - Concomitant carbamazepine and dextropropoxyphene administration significantly increases carbamazepine concentrations and may result in moderate to severe neurotoxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnoea, seizures, coma).

Orphenadrine - Confusion, anxiety and tremors have been reported in a few patients receiving dextropropoxyphene concomitantly with orphenadrine.

ADVERSE REACTIONS

The most commonly reported adverse reactions are dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients and some of these adverse reactions may be alleviated if the patient lies down.

Other less frequent to rarely reported adverse reactions are light headedness, headache, weakness, euphoria, dysphoria, hallucinations, constipation, abdominal pain, minor visual disturbances, skin rashes, allergic reactions, thrombocytopenia and leukopenia.

Dextropropoxyphene has been associated with abnormal liver function tests and more rarely, with instances of reversible jaundice (including cholestatic jaundice).

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

Adults: One capsule every 4 hrs as needed, maximum 6 capsules/day or
dextropropoxyphene 600 mg/day.

Reduce the total daily dosage in patients with hepatic or renal impairment.

OVERDOSAGE

Initial consideration should be given to the management of the CNS effects of
dextropropoxyphene overdosage. Resuscitative measures should be initiated promptly.

Symptoms of Dextropropoxyphene Overdosage-The manifestations of acute
overdosage with dextropropoxyphene are those of opioid overdosage. The patient
is usually somnolent but may be stuporous or comatose and convulsing.
Respiratory depression is characteristic. The ventilatory rate and/or tidal volume is
degraded, which results in cyanosis and hypoxia. Pupils, initially pinpoint, may
become dilated as hypoxia increases. Cheyne-Stokes respiration and apnoea may
occur. Blood pressure and heart rate are usually normal initially, but blood
pressure falls and cardiac performance deteriorates, which ultimately results in
pulmonary oedema and circulatory collapse, unless the respiratory depression is
corrected and adequate ventilation is restored promptly. Cardiac arrhythmias and
conduction delay may be present. A combined respiratory-metabolic acidosis
occurs owing to retained CO₂ (hypercapnia) and to lactic acid formed during
anaerobic glycolysis. Acidosis may be severe if large amounts of salicylates have
also been ingested. Death may occur. Subacute painful myopathy has been
reported following chronic dextropropoxyphene overdosage.

Treatment of Dextropropoxyphene Overdosage-Attention should be directed first to
establishing a patent airway and to restoring ventilation. Mechanically assisted
ventilation, with or without oxygen, may be required, and positive pressure
respiration may be desirable if pulmonary oedema is present. The narcotic
antagonist naloxone will markedly reduce the degree of respiratory depression, and
0.4 to 2 mg should be administered promptly, preferably intravenously. If the
desired degree of counteraction with improvement in respiratory functions is not
obtained, naloxone should be repeated at two to three minute intervals. 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 dextropropoxyphene
toxicity should be questioned. Naloxone may also be administered by continuous
intravenous infusion.

Treatment of Dextropropoxyphene Overdosage in Children-The usual initial dose of
naloxone in children is 0.01 mg/kg body weight given intravenously. If this dose
does not result in the desired degree of clinical improvement, a subsequent
increased dose of 0.1 mg/kg body weight may be administered. If an I.V. route of
administration is not available, naloxone may be administered IM or
subcutaneously in divided doses. If necessary, naloxone can be diluted with Sterile
Water for Injection.
Blood gases, pH, and electrolytes should be monitored in order that acidosis and any electrolyte disturbance present may be corrected promptly. Acidosis, hypoxia, and generalised CNS depression predispose to the development of cardiac arrhythmias. Ventricular fibrillation or cardiac arrest may occur and necessitate the full complement of cardiopulmonary resuscitation (CPR) measures. Respiratory acidosis rapidly subsides as ventilation is restored and hypercapnia eliminated, but lactic acidosis may require intravenous bicarbonate for prompt correction.

Electrocardiographic monitoring is essential. Prompt correction of hypoxia, acidosis, and electrolyte 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 dextropropoxyphene. Dialysis is of little value in poisoning due to dextropropoxyphene. Efforts should be made to determine whether other agents, such as alcohol, barbiturates, tranquillisers, or other CNS depressants, were also ingested, since these increase CNS depression as well as cause specific toxic effects.

**ANIMAL TOXICOLOGY**

The acute lethal doses of the hydrochloride and napsylate salts of dextropropoxyphene were determined in four species. The results shown in Figure 2 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 dextropropoxyphene napsylate.

![Figure 2: Acute oral toxicity of dextropropoxyphene](image_url)

<table>
<thead>
<tr>
<th>Species</th>
<th>Dextropropoxyphene Hydrochloride</th>
<th>Dextropropoxyphene Napsylate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>282 ± 39</td>
<td>915 ± 163</td>
</tr>
<tr>
<td></td>
<td>0.75</td>
<td>1.62</td>
</tr>
<tr>
<td>Rat</td>
<td>230 ± 44</td>
<td>647 ± 95</td>
</tr>
<tr>
<td></td>
<td>0.61</td>
<td>1.14</td>
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<tr>
<td>Rabbit</td>
<td>ca.82</td>
<td>183</td>
</tr>
<tr>
<td></td>
<td>0.22</td>
<td>0.32</td>
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<tr>
<td>Dog</td>
<td>ca.100</td>
<td>183</td>
</tr>
<tr>
<td></td>
<td>0.27</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Some indication of the relative insolubility and retarded absorption of dextropropoxyphene napsylate was obtained by measuring plasma
dextropropoxyphene levels in two groups of four dogs following oral administration of equimolar doses of the two salts. As shown in Figure 3, the peak plasma concentration observed with dextropropoxyphene hydrochloride was much higher than that obtained after administration of the napsylate salt.

Although none of the animals in this experiment died, three of the four dogs given dextropropoxyphene hydrochloride exhibited convulsive seizures during the time interval corresponding to the peak plasma levels. The four animals receiving the napsylate salt were mildly ataxic but not acutely ill.

Figure 3. Plasma dextropropoxyphene concentrations in dogs following large doses of the hydrochloride and napsylate salts.

PRESENTATION AND STORAGE CONDITIONS

DOLOXENE is supplied as capsules each containing 100 mg dextropropoxyphene napsylate. DOLOXENE is available in blister packs of 10 capsules.

Store below 25ºC.

NAME AND ADDRESS OF THE SPONSOR

Aspen Pharmacare Australia Pty Ltd
34-36 Chandos Street
St Leonards, NSW 2065 Australia

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription only medicine.

DATE OF APPROVAL

TGA Approval: 30 June 2009

Date of most recent amendment: 22 February 2012