PRODUCT INFORMATION

PARADEX

NAME OF THE DRUG:

Dextropropoxyphene Hydrochloride; Paracetamol

Structural Formulae

Dextropropoxyphene Hydrochloride

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\text{Dextropropoxyphene Hydrochloride}
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CAS-1639-60-7

Paracetamol

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\text{Paracetamol}
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CAS-103-90-2

DESCRIPTION:

Dextropropoxyphene Hydrochloride 32.5 mg, Mol. Wt. 375.9, \(C_{22}H_{29}NO_2\).HCl is (1S, 2R)-1-benzyl-3-dimethylamino-2-methyl-1-phenylpropyl propionate hydrochloride.

Paracetamol 325 mg, Mol. Wt. 151.2, \(C_8H_9NO_2\) is N-(4-hydroxyphenyl) acetamide.

Dextropropoxyphene hydrochloride occurs as a white or slightly yellow powder, odourless, and with a bitter taste. It is soluble in 0.3 parts of water, 1 in 1 - 5 parts of alcohol (95%) and 1 in 0.6 parts of chloroform. It is insoluble in solvent ether. It has a melting point of about 165°. Paracetamol occurs as white crystals or a white crystalline powder; odourless and with a bitter taste. It is soluble 1 in 70 parts of water, 1 in 7 parts of alcohol (95%), 1 in 13 parts of acetone, 1 in 40 parts of glycerol, and 1 in 9 parts of propylene glycol; it is also soluble in solutions of the alkali hydroxides. It has a melting point of 169° to 172°.

Excipients:

Lactose BP, Starch-wheat, Starch−pregelatinised wheat, Silica−colloidal anhydrous, Talc-purified, Ethylcellulose, Sodium starch glycollate, Povidone and Magnesium stearate.
PHARMACOLOGY:

Actions:

*Dextropropoxyphene hydrochloride* 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 hydrochloride is from two thirds to equal that of codeine.

*Paracetamol* is a non-opioid analgesic and an anti-pyretic. The analgesic effect of paracetamol is thought to be due to the inhibition of prostaglandin synthesis in the central nervous system and the periphery and, to a lesser extent, by blocking the pain impulse generation in the periphery. The antipyretic effect is due to a central action on the hypothalamic heat regulating centre to produce peripheral vasodilatation and subsequent heat loss.

The combination of dextropropoxyphene with paracetamol produces greater analgesia than that produced by either drug administered alone.

Pharmacokinetics:

*Dextropropoxyphene* is readily absorbed from the gastrointestinal tract but is subject to considerable first pass metabolism. Equimolar doses of dextropropoxyphene hydrochloride or dextropropoxyphene 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 2½ hours. After a 65 mg oral dose of dextropropoxyphene hydrochloride, peak plasma levels of 0.05 to 0.1 mcg/ml are achieved.

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 the antiarrhythmic agents, such as lignocaine and quinidine. In animal studies in which dextropropoxyphene and norpropoxyphene were continually 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.

*Paracetamol* is absorbed rapidly and completely from the small intestine after oral administration. Peak plasma paracetamol concentrations occur 30 to 120 minutes after oral administration. It is uniformly distributed throughout most body fluids with an apparent volume of distribution of 1 to 1.2 L/kg. Plasma protein binding is negligible at the usual therapeutic concentrations but increases with increasing concentrations.

Approximately 90 to 95% of a dose of paracetamol is metabolised by the hepatic microsomal system. In adults at therapeutic doses, paracetamol is mainly conjugated with glucuronide (45-55%) or sulphate (20-30%). A minor proportion (less than 20%) is
metabolised to catechol derivatives. Paracetamol is metabolised differently by infants and children compared with adults, the sulphate conjugate being predominant.

Paracetamol is excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol with 85-90% of the dose being eliminated within the urine within 24 hours of ingestion. The elimination half-life of paracetamol varies from about 1 to 4 hours. Food delays paracetamol absorption.

**INDICATIONS:**
Relief of mild to moderate pain.

**CONTRAINDICATIONS:**
Known hypersensitivity to either constituent.

Concurrent use of alcohol.

Concurrent use of other paracetamol containing products.

**WARNINGS:**
• **DO NOT PRESCRIBE DEXTROPROPOXYPHENE FOR PATIENTS WHO ARE SUICIDAL OR PRONE TO 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 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. In patients who are depressed or suicidal, consideration should be given to the use of non-opioid analgesics. Patients should be cautioned about the Concurrent 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 concurrent 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 tranquillizers, alcohol, and other CNS-active drugs. Caution should be exercised in prescribing dextropropoxyphene hydrochloride for such patients (see Management of 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, less frequently, physical dependence and tolerance. Dextropropoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. 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:
Use in Patients with Hepatic or Renal Impairment
Dextropropoxyphene should be administered with caution to patients with renal or hepatic impairment since higher serum concentrations or delayed elimination may occur.

Use in Patients with Respiratory Impairment
Dextropropoxyphene should be administered with caution to patients with respiratory impairment as it may depress respiration.

Use in Pregnancy – Pregnancy (Category C)
PARADEX should not be used in pregnant women unless, in the judgement of the physician, the potential benefits outweigh the possible hazards.

Dextropropoxyphene may cause respiratory depression in the newborn infant. Safe use in pregnancy has not been established relative to possible adverse effects on foetal development. Instances of withdrawal symptoms in the neonate have been reported following usage during pregnancy.

Paracetamol can cross the placenta. However in rats and mice no teratogenic effects have been observed after doses of up to 250 mg/kg.

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.

Paracetamol is excreted in breast milk. The amount available for ingestion by the infant has been reported variously as less than 0.1% of a single 500 mg dose and as 0.04 to 0.23% of a single 650 mg dose. Maternal ingestion of paracetamol in usual analgesic doses does not appear to present a risk to the nursing infant.

Use in Children
PARADEX is not recommended for use in children. The safety and effectiveness of dextropropoxyphene in children has not been established.

Use in the Elderly
The elderly are more likely to have age related renal impairment and increased susceptibility to the respiratory depressant effects of opioid analgesics. The rate of dextropropoxyphene metabolism may be reduced in some patients. An increased dosing interval or dose reduction should be considered.
Carcinogenicity, Mutagenicity, Impairment of Fertility
Clinical toxicity studies in animals have shown that high doses of paracetamol cause testicular atrophy and inhibition of spermatogenesis; the relevance of this finding to use in humans is not known.

Drug interactions
General – Dextropropoxyphene may inhibit the hepatic metabolism of concurrently administered drugs. Should this occur, higher serum concentrations of the concurrently 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 anti-depressants, anti-convulsants, or warfarin like drugs.

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

CNS Stimulants – The convulsant action of dextropropoxyphene may be enhanced by CNS stimulants.

Warfarin – Concurrent warfarin and dextropropoxyphene administration may increase serum concentrations of warfarin. Paracetamol may affect prothrombin time in patients receiving anticoagulant therapy. Warfarin dosage adjustments may be required.

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

Ritonavir – Concurrent ritonavir and dextropropoxyphene administration may increase serum concentrations of dextropropoxyphene resulting in an increased risk of CNS depression or other serious adverse effects.

Beta-Blockers – Oral bioavailability of metoprolol and propanolol may increase when they are given Concurrently with dextropropoxyphene.

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

Doxepin – Concurrent administration of dextropropoxyphene and doxepin may double steady state doxepin and desmethyldoxepin plasma concentrations. This may increase doxepin toxicity (sedation, lethargy, dry mouth, urinary retention).

Chloramphenicol – Concurrent administration of paracetamol and chloramphenicol may increase chloramphenicol serum concentrations.

Cholestyramine – Concurrent administration of paracetamol and cholestyramine can lower plasma paracetamol plasma concentrations.

Diflunisal – Concurrent administration of paracetamol and diflunisal can increase paracetamol plasma concentrations by up to 50%.

Phenytoin – Concurrent administration of paracetamol and phenytoin can increase the metabolism of paracetamol by more than 40% and decrease its half-life by about 25%.
There is an increased risk of paracetamol hepatotoxicity with Concurrent administration of these two drugs.

**Lamotrigine** – Concurrent administration of paracetamol and lamotrigine may slightly increase the elimination of lamotrigine.

**Metyrapone** – Concurrent administration of paracetamol and metyrapone may decrease the elimination of paracetamol.

**Probenecid** – Concurrent administration of paracetamol and probenecid may prolong the half-life and decrease the clearance of paracetamol. The clinical significance of this is unclear.

**Sulfinpyrazone** – Concurrent administration of paracetamol and sulfinpyrazone can increase the metabolism of paracetamol.

**Zidovudine** – Concurrent administration of paracetamol and zidovudine has been associated with an increased incidence of neutropenia, especially during chronic therapy.

**ADVERSE REACTIONS:**
The most commonly reported adverse reactions are dizziness, sedation, nausea, and vomiting. 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, hepatic impairment, minor visual disturbances, skin rashes, allergic reactions, thrombocytopenia, leucopenia, pancytopenia, neutropenia, agranulocytosis.

Hepatic dysfunction has been reported in association with both dextropropoxyphene and paracetamol. Dextropropoxyphene 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 paracetamol overdose (see Management of Overdosage). In chronic alcohol abusers this has been reported rarely with short term use of paracetamol doses of 2.5 to 10g/day. Fatalities have occurred.

The chronic ingestion of dextropropoxyphene in doses exceeding 720 mg per day has caused toxic psychoses and convulsions. A single dose of 1200 mg of dextropropoxyphene has caused convulsions.

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

Subacute painful myopathy has occurred following chronic dextropropoxyphene overdose.

**DOSAGE & ADMINISTRATION:**
PARADEX is given orally. The usual adult dose is 1 to 2 tablets four hourly as needed for pain. A dose of 2 tablets will provide 65 mg of dextropropoxyphene hydrochloride and 650 mg of paracetamol.

The maximum recommended daily dose of dextropropoxyphene hydrochloride is 390mg.
The maximum recommended daily dose of paracetamol is 4g.

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

**OVERDOSAGE:**
There are a disturbing number of fatalities from either accidental or intentional overdosage with dextropropoxyphene, many emphasising the rapidity with which death ensues. The first priority is therefore management of the CNS effects of dextropropoxyphene overdosage. Resuscitative measures should be initiated promptly.

*Symptoms of Dextropropoxyphene Overdose* – The manifestations of acute overdosage with dextropropoxyphene are similar to those of narcotic 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 decreased, 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 (hypercapnoea) and to lactic acid formed during anaerobic glycolysis. Death may occur.

*Treatment of Dextropropoxyphene Overdose* – Attention should be directed first to establishing a patient 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 2 to 3 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 Overdose in Children* – The usual initial dose of naloxone in children is 0.01mg/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 IV 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 hypercapnoea 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 absorb 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, tranquillizers, or other CNS depressants, were also ingested, since these increase CNS depression as well as cause specific toxic effects.

Symptoms of Paracetamol Overdosage – Shortly after oral ingestion of an overdose of paracetamol and for the next 24 hours, anorexia, nausea, vomiting, sweating, general malaise, hypotension and abdominal pain can occur. The most serious adverse effect of the acute overdosage is a dose dependent, potentially fatal hepatic necrosis. In adults, hepatotoxicity may occur after ingestion of 10 to 15g of paracetamol; a dose of 25g or more is potentially fatal. Symptoms during the first 2 days of acute poisoning by paracetamol do not reflect the potential seriousness of the intoxication. The major manifestations of liver failure such as jaundice, hypoglycaemia, and metabolic acidosis may take at least 3 days to develop. Death from hepatic failure may result 3 to 7 days after overdosage.

Acute renal failure may accompany the hepatic dysfunction and has been noted in patients who do not exhibit signs of fulminant hepatic failure. Typically, renal impairment is more apparent 6 to 9 days after ingestion of the overdose.

Treatment of Paracetamol Overdosage – In cases of overdosage, methods of reducing the absorption of ingested drug are important. Gastric lavage is essential even if several hours has elapsed. Prompt administration of activated charcoal by mouth may reduce absorption. Early measurement of paracetamol serum concentration is essential. The antidote, N-acetylcysteine should be administered as early as possible and preferably within 16 hours of the overdose for optimal results, but in any case, within 24 hours.

PRESENTATION:
Tablets, (white, scored) 20’s, in blister packs

STORAGE:
Store below 25°C

POISON SCHEDULES:
S4, except S8 in TAS.

SPONSOR:
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