PRODUCT INFORMATION

DI-GESIC®
(dextropropoxyphene hydrochloride with paracetamol)

NAME OF THE MEDICINE

DI-GESIC® (dextropropoxyphene hydrochloride with paracetamol).

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. DI-GESIC is contraindicated in patients with congenital long QT syndrome or known acquired QT interval prolongation. DI-GESIC 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, DI-GESIC MUST be ceased immediately.
DESCRIPTION

DI-GESIC:
Each tablet of DI-GESIC (dextropropoxyphene hydrochloride with paracetamol) contains 32.5 mg of the analgesic agent dextropropoxyphene hydrochloride and 325 mg of the analgesic-antipyretic agent paracetamol. DI-GESIC contains the inactive ingredients: starch-maize, starch-pregelatinised maize, magnesium stearate, hypromellose, glycerol and titanium dioxide.

Dextropropoxyphene:
Chemically it is (+)-(IS,2R)-1-benzyl-3-dimethylamino-2-methyl-l-phenylpropyl propionate hydrochloride and its molecular formula is C\textsubscript{22}H\textsubscript{29}NO\textsubscript{2}HCl. Dextropropoxyphene hydrochloride is an odourless, white crystalline powder with a bitter taste. It is freely soluble in water and has a molecular weight of 375.9. The CAS number for dextropropoxyphene hydrochloride is 1639-60-7.

Dextropropoxyphene hydrochloride has the following chemical structure:

![Chemical Structure of Dextropropoxyphene Hydrochloride]

Paracetamol:
Paracetamol is a white crystalline powder. Chemically it is 4'-Hydroxyacetanilide; N-(4-Hydroxyphenyl) acetamide and its molecular formula is C\textsubscript{8}H\textsubscript{9}NO\textsubscript{2}. It is very slightly soluble in water and has a molecular weight of 151.2. The CAS registry number for paracetamol is 103-90-2.

Paracetamol has the following chemical structure:

![Chemical Structure of Paracetamol]

PHARMACOLOGY

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 anti-pyretic effect is due to a central action on the hypothalamic heat regulating centre to produce peripheral vasodilation 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 2 ½ 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 metabolised 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 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 sulfate (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 sulfate conjugate being predominant.

Paracetamol is excreted in the urine mainly as the glucoronide and sulfate conjugates. Less than 5% is excreted as unchanged paracetamol with 85-90% of the dose being eliminated in 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**

DI-GESIC is indicated for the relief of mild to moderate pain in patients who do not respond adequately to other analgesics.

**CONTRAINDICATIONS**

Hypersensitivity to dextropropoxyphene or paracetamol.

Concomitant use of alcohol in patients with abuse potential or a history of alcohol or substance abuse.

Concomitant use of other paracetamol containing products where the total daily intake of paracetamol will exceed 4 g per day.

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 DI-GESIC 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 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, 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

DI-GESIC 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 40mL/min) and/or ECG results of concern, DI-GESIC must be ceased immediately.

**Use in Pregnancy**—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.

**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 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, tranquillizers, sedative-hypnotics and other central nervous system depressants has additive depressant effects and the patient should be so advised. Patients taking DI-GESIC 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. Paracetamol may affect prothrombin time in patients receiving anticoagulant therapy. 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. Some of these side effects may be alleviated if the patient lies down.

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

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 overdoses of paracetamol (see OVERDOSAGE). In chronic ethanol abusers, this has been reported rarely with short-term use of paracetamol doses of 2.5 to 10 g/day. Fatalities have occurred.

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 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.

DOSAGE AND ADMINISTRATION

Adults: 2 tablets every 4 hours as needed, maximum 12 tablets/day or dextropropoxyphene 390mg/day, paracetamol 3.9g/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 similar to 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 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. 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 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 Overdosage in Children**—The 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 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 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, tranquilizers, 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, diaphoresis, general malaise, and abdominal pain have been noted. The patient may then present no symptoms, but evidence of liver dysfunction may be apparent during the next 24 to 48 hours, with elevated serum transaminase and lactic dehydrogenase levels, an increase in serum bilirubin concentrations and a prolonged prothrombin time. 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 adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 g and fatalities with less than 15 g. Serious toxicity or fatalities are infrequent in children, possibly due to the differences in the way they metabolise paracetamol. An acute overdosage of less than 150 mg/kg in children has not been associated with hepatic toxicity. Nevertheless the measures outlined to treat paracetamol overdosage should be initiated in any adult or child suspected of overdosing.

Because clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours postingestion, liver function studies should be obtained initially and repeated at 24-hour intervals. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise.

In cases of overdosage, methods of reducing the absorption of the ingested drug are important. Gastric lavage is essential even if several hours have elapsed since ingestion. Prompt administration of activated charcoal by mouth may reduce absorption. Patients' estimates of the quantity of a drug ingested are notoriously unreliable. Therefore, if a paracetamol overdose is suspected, a serum paracetamol assay should be obtained as early as possible, but no sooner than 4 hours following ingestion. The antidote N-acetylcysteine should be administered as early as possible, preferably within 16 hours of the overdose ingestion for optimal results. Following recovery there are no residual structural or functional hepatic abnormalities.

**PRESENTATION AND STORAGE CONDITIONS**

DI-GESIC is a white film coated capsule shaped tablet, upper surface embossed “DIGESIC”, lower surface plain. Each tablet contains 32.5 mg dextropropoxyphene hydrochloride and 325 mg paracetamol. DI-GESIC is available in blister packs of 20 for retail supply and starter packs of 2.

Store below 25°C.

**NAME AND ADDRESS OF SPONSOR**

Aspen Pharmacare Australia Pty Ltd
34-36 Chandos Street
St Leonards, NSW 2065
Australia
POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine).

DATE OF APPROVAL

TGA Approval: 19 October 2004

Date of most recent amendment: 22 February 2012