

Data Sheet

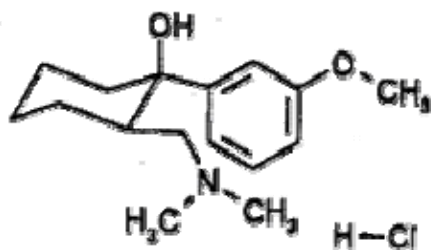
Tramadol 50mg capsules

Tramadol hydrochloride 50mg capsules

Description

Tramadol hydrochloride 50mg capsules contain tramadol hydrochloride which is (\pm) - cis-2-(dimethylaminomethyl)-1-(3-methoxyphenyl)-cyclohexanol hydrochloride. Tramadol hydrochloride is an odourless, white to off-white crystalline powder that is readily soluble in both water and ethanol and has a pKa of 9.41. The water/n-octanol partition coefficient is 1.35 at pH 7. It belongs to the synthetic analgesics class and has opioid-like activity, with the formula: $C_{16}H_{25}NO_2 \cdot HCl$. MW = 299.84.

The structural formula of tramadol hydrochloride is:-



The CAS Registry Number is 36282-47-0.

Presentation

Tramadol hydrochloride 50mg capsules: Green/Yellow coloured hard gelatin capsules, size 3 filled with homogeneous white to off-white powder.

The capsules also contain the inactive ingredients microcrystalline cellulose, sodium starch glycolate, colloidal anhydrous silica, magnesium stearate and purified water. Excipients in the capsule shell are: Yellow ferric oxide (E172), Indigo carmine (E132), Titanium dioxide (E171), Sodium lauryl sulfate, Methyl parahydroxybenzoate (E218), Propyl parahydroxybenzoate (E216) & Gelatin.

Action

Pharmacodynamics

Tramadol is a centrally-acting synthetic analgesic of the aminocyclohexanol group with opioid-like effects. It is not derived from natural sources, nor is it chemically related to opiates. Although pre-clinical testing has not completely explained the mode of action, at

least two complementary mechanisms appear applicable: binding to μ -opioid receptors and inhibition of re-uptake of noradrenaline and serotonin. The opioid-like activity of tramadol derives from low affinity binding of the parent compound to μ -opioid receptors and higher affinity binding of the principal active metabolite, O-desmethyltramadol, denoted M1, to μ -opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ -opioid binding. The contribution to human analgesia of tramadol relative to M1 is unknown.

Both animal and human studies have shown that antinociception induced by tramadol is only partially antagonised by the opiate antagonist naloxone. In addition, tramadol has been shown to inhibit re-uptake of noradrenaline and serotonin in vitro, as have some other opioid analgesics. These latter mechanisms may contribute independently to the overall analgesic profile of tramadol.

The analgesic effect is dose-dependant, but the relationship between serum concentrations and analgesic effect varies considerably between individuals. In one study, the median serum concentration of tramadol required for effective post-operative analgesia was 300 ng/mL, with individual values ranging from 20 to 990 ng/mL.

Apart from analgesia, tramadol may produce other symptoms similar to that of opioids including: dizziness, somnolence, nausea, constipation, sweating and pruritus. However, tramadol causes significantly less respiratory depression than morphine. In contrast to morphine, tramadol has not been shown to cause histamine release. At therapeutic doses, tramadol has no clinically significant effect on heart rate, left ventricular function or cardiac index. Orthostatic changes in blood pressure have been observed.

Pharmacokinetics

Tramadol is administered as a mixture of two stereoisomers; the following information refers to the combined concentration of both isomers. Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range.

Absorption

Tramadol is rapidly and almost completely absorbed after oral administration of 50 mg capsules following a mean absorption delay (t_0) of approximately thirty minutes. The absorption half-life ($t_{1/2}$) is 23 ± 11 minutes. After oral administration of two 50 mg capsules, the mean absolute bioavailability (f_{abs}) is 68-72%, and the peak serum level (C_{max}) is reached two hours (range one to three) after administration. The mean peak plasma concentration (C_{max}) is approximately 280 ng/mL after oral administration of two capsules. At this time, the mean serum concentration after intravenous injection is 1.46 times higher, amounting to approximately 410 ng/mL.

Oral administration of tramadol with food does not significantly affect its rate or extent of absorption. Therefore tramadol can be administered without regard to food.

After repeated oral administration of 50 mg and 100 mg tramadol capsules at six hourly intervals, steady state is reached 30 to 36 hours after the first administration and the bioavailability is greater than 90%. The plasma concentrations at steady state exceeded by 52% and 36% those extrapolated from the single dose administration studies with 50 mg and 100 mg capsules, respectively. This can be explained by first pass metabolic saturation.

Distribution

Tramadol is rapidly distributed in the body, with a volume of distribution of 2 - 3 L/kg in young adults. The volume of distribution is reduced by about 25% in those aged over 75 years. Plasma protein binding is about 20% and is independent of concentration up to 10 µg/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range.

Tramadol crosses the placental and blood-brain barriers. Very small amounts of tramadol and M1 are found in breast milk (0.1% and 0.02% respectively of the administered dose).

Metabolism

Tramadol is extensively metabolised after oral administration. The major metabolic pathways appear to be N - and O -demethylation and glucuronidation or sulfation in the liver. Only O -desmethyltramadol (M1) is pharmacologically active. Production of M1 is dependent on the CYP2D6 isoenzyme of cytochrome P450. Patients who metabolise drugs poorly via CYP2D6 may obtain reduced benefit from tramadol, due to reduced formation of M1. N-demethylation is catalysed by the CYP3A4 isoenzyme of cytochrome P450. The inhibition of one or both types of the isoenzymes CYP3A4 and CYP2D6 involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolite.

Excretion

Tramadol and its metabolites are excreted mainly by the kidneys, with a cumulative renal excretion (tramadol and metabolites) of approximately 95%. In young adults approximately 15 - 19% of an administered dose of tramadol is excreted in the urine as unmetabolised drug. In the elderly, this increases to about 35%. Biliary excretion is of little importance. In young adults, the half-life of tramadol is 5 - 7 h and the half-life of M1 is 6 - 8 h. Total clearance is approximately 430 - 610 mL/min.

Pharmacokinetics in patients with hepatic or renal impairment

Elimination of tramadol and M1 is impaired in patients with hepatic or renal impairment (see WARNINGS AND PRECAUTIONS). In patients with hepatic impairment, the mean half-life of tramadol was found to be 13 h (range up to 19 h), and the mean half-life of M1 was 19 h (range up to 36 h).

In patients with renal impairment including subjects with considerably decreased CLCr [$< 5\text{mL}/\text{min}$] the mean half-life of tramadol was 11 h (range up to 20 h), and the mean half life of M1 was 17 h (range up to 43 h).

Pharmacokinetics in the elderly

In the elderly (age over 75 years), the volume of distribution of tramadol is decreased by 25% and clearance is decreased by 40%. As a result, tramadol C_{max} and total exposure are increased by 30% and 50%, respectively, but the half-life of tramadol is only slightly prolonged (by 15%).

Indications

Relief of moderate to severe pain.

Dosage and Administration

The dose of tramadol should be titrated to the severity of the pain and the clinical response of the individual patient. Tramadol is approved for use in adults, adolescents, and children over the age of 2 years. See the Paediatric Use section below for children aged between 2 and 12 years.

For the treatment of moderate pain Tramadol 50 - 100 mg administered two or three times daily may be sufficient. Tramadol 50 mg may be adequate as the initial dose for moderate pain.

For moderate to severe pain, 50 - 100 mg as needed for relief, every four to six hours may be administered. Tramadol 100mg is usually more effective as the initial dose for more severe pain.

The maximum daily dose should not exceed 400mg per day.

Paediatric use - On account of their high dosage strengths, Tramadol capsules are not recommended for use in children below the age of 12 years.

Use in the elderly - In subjects over the age of 75 years, serum concentrations are slightly elevated and the elimination half-life is slightly prolonged. Subjects in this age group are also expected to vary more widely in their ability to tolerate adverse drug effects. Daily doses in excess of 300 mg are not recommended in patients over 75 years.

Renal insufficiency - in patients with renal insufficiency the elimination of tramadol is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements. In cases of severe renal insufficiency tramadol is not recommended. Since only 7% of an administered dose is removed by haemodialysis, dialysis patients can receive their regular dose on the day of dialysis.

Hepatic insufficiency - In hepatic impairment, the initial oral dose of tramadol is 50 mg of the immediate release formulation. Depending on the severity of the impairment and individual clinical response, the recommended dosage interval (4-6 hours) may require to be extended, and/or the dose level titrated as required.

Contraindications

Tramadol is contraindicated in:

- individuals with known hypersensitivity to tramadol or any excipients
- acute intoxication with alcohol, hypnotics, analgesics, opioids or psychotropic drugs
- patients who are taking MAO inhibitors or who have taken them within the last 14 days
- known hypersensitivity to opioids
- patients with uncontrolled epilepsy or epilepsy not adequately controlled by treatment.

Tramadol must not be used for narcotic withdrawal treatment.

Warnings And Precautions

Acute abdominal conditions

The administration of tramadol may complicate the clinical assessment of patients with acute abdominal conditions.

Respiratory depression

Tramadol should be administered cautiously in patients at risk of respiratory depression. When large doses of tramadol are administered with anaesthetic medications or alcohol, respiratory depression may result. Cases of intra-operative respiratory depression, usually with large intravenous doses of tramadol and with concurrent administration of respiratory depressants, have been reported.

Increased intracranial pressure or head trauma

Tramadol should be used with caution in patients with increased intracranial pressure, head injury, shock or a reduced level of consciousness of uncertain origin. Pupillary changes (miosis) from tramadol may obscure the existence, extent, or course of intracranial pathology. Clinicians should also maintain a high index of suspicion for adverse drug reaction when evaluating altered mental status in these patients if they are receiving tramadol.

Serotonin syndrome (serotonin toxicity)

Tramadol is known to cause Serotonin syndrome when used concomitantly with other medicines that increase serotonin levels. The presence of another drug that increases

serotonin by any mechanism should alert the treating physician to the possibility of an interaction. Signs of serotonin syndrome may be, for example, confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea. Withdrawal of the serotonergic medicines usually brings about a rapid improvement. Drug treatment depends on the nature and severity of the symptoms (See *Interactions*).

Renal and hepatic disease

With the prolonged half-life in these conditions, achievement of steady state is delayed, so that it may take several days for elevated plasma concentrations to develop.

Renal disease

In patients with renal insufficiency the elimination of tramadol is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements. In cases of severe renal insufficiency tramadol is not recommended. As tramadol is removed very slowly by haemodialysis or haemofiltration, post-dialysis administration to maintain analgesia is not usually necessary.

Hepatic disease

Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver. In cirrhotic patients, dosage reduction is recommended (see DOSAGE AND ADMINISTRATION).

Effects on ability to drive and use machinery

Due to its sedative effect, patients should be advised to avoid driving or operating machinery whilst taking tramadol.

Patients physically dependent on opioids

Tramadol is not recommended as a substitute in opioid-dependent patients. Although tramadol is an opiate-agonist, it cannot suppress opioid withdrawal symptoms. Animal experiments have shown that under certain circumstances the administration of tramadol may provoke a withdrawal syndrome in opioid-dependent monkeys. Because of the difficulty in assessing dependence in patients who have previously received substantial amounts of opioid medications, caution should be used in the administration of tramadol to such patients.

In patients with a tendency for drug abuse or dependence, treatment with tramadol should only be carried out for short periods under strict medical supervision.

Cases of dependence and abuse of tramadol have been reported rarely.

Seizure risk

Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of tramadol exceed the recommended upper daily dose limit. In addition, tramadol may increase the seizure risk in patients taking other medication that lowers the seizure threshold (see Interactions with other drugs). Patients with epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling circumstances.

Anaphylactoid reactions

Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving tramadol. These reactions often occur following the first dose. Other reported reactions include pruritus, hives, bronchospasm and angioedema.

Intra-operative use

In one study using nitrous oxide/tramadol anaesthetic technique (with only intermittent administration of enflurane "as required"), tramadol was reported to enhance intra-operative recall. Hence its use during potentially very light levels of general anaesthesia should be avoided. Two recent studies of tramadol administration during anaesthesia comprising continuous administration of isoflurane did not show clinically significant lightening of anaesthetic depth or intra-operative recall. Therefore, providing the current practice of administering continuous, potent (volatile or intravenous) anaesthetic agent is followed, tramadol may be used intra-operatively in the same way as other analgesic agents are routinely used.

Long-term use

Tramadol has been studied in controlled clinical trials for periods of up to three months. In one small uncontrolled study, patients with cancer pain received a dose of 150 mg tramadol per day for up to six months. Beyond six months no clinical studies investigating the safety and efficacy of tramadol are available.

When tramadol treatment of pain is required long-term, careful and regular monitoring should be carried out to establish whether, and to what extent, ongoing treatment is necessary.

Carcinogenesis, mutagenesis and impairment of fertility

Tramadol was not mutagenic in the following assays: Ames Salmonella microsomal activation test, CHO/HPRT mammalian cell assay, mouse lymphoma assay (in the presence of metabolic activation), dominant lethal mutation tests in mice, chromosome aberration test in Chinese hamster cells, and bone marrow micronucleus tests in mice and Chinese hamster cells. Weakly mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay and micronucleus tests in rat cells. Overall, the

weight of evidence from these tests indicates tramadol does not possess a genotoxic risk to humans.

A slight, but statistically significant increase in two common murine tumours (pulmonary and hepatic) was observed in a mouse carcinogenicity study, particularly in aged mice dosed orally up to 30 mg/kg for approximately two years. Although the study was not conducted using the Maximum Tolerated Dose, or at exposure levels expected in clinical use, this finding is not believed to suggest risk in humans. No such findings occurred in a rat carcinogenicity study.

No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg.

Use in pregnancy - Category C

There are no adequate and well-controlled studies with tramadol in pregnant women, therefore, tramadol should not be used during pregnancy. Studies in animals using IV or IM routes of administration have not been conducted. Tramadol has been shown to be embryotoxic and foetotoxic in mice, rats and rabbits in maternally toxic doses of 120 mg/kg in mice, or higher in rats and 75 mg/kg in rabbits, but was not teratogenic at these dose levels. No harm to the foetus due to tramadol was seen at doses that were not maternally toxic. No drug-related teratogenic effects were observed in progeny of mice, rats or rabbits treated with tramadol (75 mg/kg for rats or 175 mg/kg for rabbits). Embryo and foetal toxicity consisted primarily of decreased foetal weights, skeletal ossification and increased supernumerary ribs at maternally toxic dose levels. Transient delays in development or behavioural parameters were also seen in pups from rat dams allowed to deliver. Embryo and foetal lethality were reported only in one rabbit study at 300 mg/kg, a dose that would cause extreme maternal toxicity in the rabbit.

In peri- and post-natal studies in rats, progeny of dams receiving oral (gavage) dose levels of 50 mg/kg or greater had decreased weights and pup survival was decreased early in lactation at 80 mg/kg (6-10 times the maximum human dose). No toxicity was observed for progeny of dams receiving 8, 10, 20, 25 or 40 mg/kg. Maternal toxicity was observed at all dose levels.

Labour and Delivery

Tramadol should not be used in pregnant women prior to or during labour unless the potential benefits outweigh the potential risks, because safe use in pregnancy has not been established. Chronic use during pregnancy may lead to neonatal withdrawal symptoms. If tramadol were to be used during labour, it may cause respiratory depression in the newborn. Tramadol has been shown to cross the placenta. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women given tramadol during labour.

The effect of tramadol, if any, on the later growth, development, and functional maturation of the child is unknown.

Use in lactation

Tramadol is not recommended during breast feeding, because its safety in infants and newborns has not been studied. Low levels of tramadol have been detected in breast milk. Following a single intravenous 100 mg dose of tramadol, the cumulative excretion in breast milk within 16 hours post-dose was 100 µg of tramadol (0.1% of the maternal dose) and 27 µg of M1.

Adverse Effects

Adverse reactions that may occur after administration of tramadol resemble those known to occur with opioids. Adverse reactions were recorded in 13,802 patients from trials with different formulations of tramadol. The nature and incidence of reactions (in CIOMS format where very common $\geq 1/10$; common $\geq 1/100$ and $<1/10$; uncommon $\geq 1/1000$ and $<1/100$; rare $\geq 1/10,000$ and $<1/1000$; and very rare $\leq 1/10,000$) were as follows:

Cardiovascular

Uncommon: orthostatic dysregulation (tendency to collapse, and cardiovascular collapse) and tachycardia, flushing

Rare: increase in blood pressure, bradycardia

Respiratory

Rare: dyspnoea

Very rare: worsening of asthma (causality not established), respiratory depression (when the recommended doses are considerably exceeded and other respiratory depressant substances are administered concomitantly)

Gastrointestinal

Very common: nausea

Common: vomiting, constipation

Uncommon: dyspepsia, diarrhoea, abdominal pain, flatulence, urge to vomit

Rare: changes in appetite

Very rare: elevated liver enzymes

Neurological

Not known: speech disorders

Very common: dizziness

Common: autonomic nervous effects (mainly dry mouth, perspiration), headache, sedation, asthenia, fatigue

Uncommon: trembling

Rare: changes in mood (usually elevation, occasionally dysphoria), paraesthesia, hallucinations, confusion, coordination disturbance, sleep disturbance, anxiety, nightmares, motor system weakness, changes in appetite, tremor, respiratory depression, seizures, involuntary muscle contractions, changes in activity (usually suppression, occasionally increase), changes in cognitive and sensorial capacity (eg. decision behaviour, perception disorders), syncope

Endocrine

Very rare: Syndrome of inappropriate antidiuretic hormone secretion characterised by hyponatraemia secondary to decreased free-water excretion

Hypersensitivity and skin

Common: sweating

Uncommon: skin reactions, pruritus, rash

Rare: shock reactions, anaphylaxis, allergic reactions

Genitourinary

Rare: micturition disorders (difficulty in passing urine and urinary retention), dysuria

Eye disorders

Not known: mydriasis

Special senses

Rare: visual disturbance (blurred vision)

The incidence of "non-specific CNS irritation" (dizziness), "autonomic nervous effects" (perspiration), "orthostatic dysregulation (tendency to collapse and cardiovascular collapse) and tachycardia and "nausea/urge to vomit/vomiting" can be increased with rapid intravenous administration and also tends to be dose dependent. No tests of significance have been performed.

Drug abuse and dependence

Although tramadol can produce drug dependence of the μ -opioid type (like codeine or dextropropoxyphene) and potentially may be abused, there has been little evidence of abuse in clinical experience to date. In clinical trials, tramadol produced some effects similar to an opioid, and at supratherapeutic doses was recognised as an opioid in subjective/behavioural studies. Part of the activity of tramadol is thought to be derived from its active metabolite, which is responsible for some delay in onset of activity and some extension of the duration of μ -opioid activity. Delayed μ -opioid activity is believed to reduce a drug's abuse liability.

Tolerance and withdrawal

Tolerance development has been reported to be relatively mild. Symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal, may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor, pyrexia, myalgia, chills and gastrointestinal symptoms. Other symptoms that have very rarely been seen with tramadol discontinuation include panic attacks, severe anxiety, hallucinations, paraesthesias, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, personalization, derealization, paranoia).

Medicine Interactions

Use with CNS depressants - Tramadol should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anaesthetic agents, phenothiazines, tranquillisers or sedative hypnotics.

The combination of tramadol with mixed opiate agonists/antagonists (eg. buprenorphine, pentazocine) is not advisable because the analgesic effect of a pure agonist may be theoretically reduced in such circumstances.

Use with other serotonergic agents - The presence of another drug that increases serotonin by any mechanism should alert the treating physician to the possibility of an interaction. In isolated cases there have been reports of serotonin syndrome in a temporal connection with the therapeutic use of tramadol in combination with other serotonergic medicines such as selective serotonin re-uptake inhibitors (SSRIs). Signs of serotonin syndrome may be, for example, confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea. Withdrawal of the serotonergic medicines usually brings about a rapid improvement. Drug treatment depends on the nature and severity of the symptoms.

Use with coumarin derivatives - Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (eg. warfarin) due to reports of increased international normalised ratio (INR) with major bleeding and ecchymoses in some patients.

Drugs which reduce the seizure threshold - Tramadol can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors, tricyclic antidepressants, antipsychotics and other seizure threshold lowering agents to cause convulsions.

Use with MAO inhibitors - Tramadol should not be used in patients who are taking MAO inhibitors or who have taken them within the last fourteen days, as tramadol inhibits the uptake of noradrenaline and serotonin (see CONTRAINDICATIONS).

Other interactions - Tramadol does not appear to induce its own metabolism in humans, since observed maximal plasma concentrations after multiple oral doses are higher than expected based on single-dose data. Tramadol is a mild inducer of selected drug metabolism pathways measured in animals.

Concomitant administration of tramadol with carbamazepine causes a significant increase in tramadol metabolism, presumably through metabolic induction by carbamazepine. Patients receiving chronic carbamazepine doses of up to 800 mg daily may require up to twice the recommended dose of tramadol.

Tramadol is metabolised to M1 by the CYP2D6 P450 isoenzyme. Drugs that selectively inhibit that isoenzyme (quinidine, phenothiazines, antipsychotic agents) may cause increased concentrations of tramadol and decreased concentrations of M1. The clinical consequences of these potential effects have not been fully investigated.

Concomitant administration of tramadol with cimetidine does not result in clinically significant changes in tramadol pharmacokinetics. Therefore no alteration of the tramadol dosage regimen is recommended.

Other drugs known to inhibit the CYP3A4 isoenzyme of cytochrome P450, such as ketoconazole and erythromycin, may inhibit the metabolism of tramadol (via N-demethylation) and probably the metabolism of the active O-demethylated metabolite (M1). The clinical importance of such an interaction has not been studied.

In a limited number of studies, the pre- or post-operative application of the antiemetic 5-HT₃ antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain.

Overdosage

Few cases of overdose with tramadol have been reported.

Symptoms

Symptoms of overdose with tramadol are similar to those of other centrally acting analgesics (opioids) and include miosis, vomiting, cardiovascular collapse, consciousness disorders including coma, convulsions, respiratory depression and respiratory arrest.

Treatment

Should overdose occur, general emergency measures should be implemented. Keep the respiratory airways open, and maintain respiration and circulation. If overdose is due to ingestion of an oral dose form, emptying the stomach by gastric lavage should be considered because of the possibility of ongoing release in the stomach.

Activated charcoal may reduce absorption of the drug if given within 1-2 hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, considerations should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

Naloxone will reverse respiratory depression, but not all symptoms caused by overdose with tramadol. Convulsions occurring in mice following the administration of toxic doses of tramadol could be suppressed with barbiturates or benzodiazepines, but were increased with naloxone. If convulsions are observed, diazepam should be given intravenously. Naloxone did not change the lethality of an overdose in mice.

Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore treatment of overdose with tramadol with haemodialysis or haemofiltration alone is not suitable for detoxification.

Storage

Store below 25°C. Store in the original package

Shelf- life

3 years when stored below 25°C.

Medicine Classification

Prescription Medicine

Package Quantities

Blister packs containing 10, 20,100 or 1000 capsules.

Further Information

Nil

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