
PRODUCT INFORMATION

DUROTRAM[®] XR

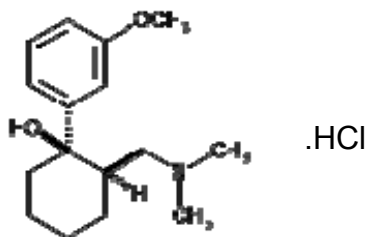
Tramadol Hydrochloride

NAME OF THE MEDICINE

The active ingredient of DUROTRAM[®] XR is tramadol hydrochloride

Chemical name: (±)-*cis*-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride or (1*RS*,2*RS*)-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride

Chemical structure:



Molecular formula: C₁₆H₂₅NO₂.HCl

Molecular weight: 299.84

CAS registry no. 36282-47-0

DESCRIPTION

Tramadol hydrochloride is a white crystalline powder with a melting point/range approximately of 180°C. It is readily soluble in water and ethanol and has a pKa of 9.41. The water/n-octanol partition coefficient is 1.35 at pH 7.

DUROTRAM[®] XR tablets are available in strengths of 100 mg, 200 mg and 300 mg tramadol hydrochloride.

DUROTRAM[®] XR tablets contain the following excipients: Contramid[®] (Hydroxypropyl distarch phosphate (E 1442)), polyvinyl acetate, povidone, sodium lauryl sulfate, xanthan gum, vegetable oil-hydrogenated, magnesium stearate, silica colloidal anhydrous, Opacode monogramming ink S-1-17823 black.

DUROTRAM[®] XR tablets are comprised of a dual-matrix delivery system with an outer compression coat which releases tramadol hydrochloride immediately and a core containing Contramid[®], which controls the release of tramadol hydrochloride.

PHARMACOLOGY

MECHANISM OF ACTION

The analgesic activity of tramadol hydrochloride is due to both parent drug and the M1 metabolite (O-desmethyl tramadol).

Tramadol is a centrally acting synthetic opioid analgesic. Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ -opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin. Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite 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. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound. (See Pharmacokinetics.)

Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin in vitro, as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of DUROTRAM[®] XR.

Apart from analgesia, tramadol administration may produce a constellation of symptoms (including dizziness, somnolence, nausea, constipation, sweating and pruritus) similar to that of opioids. In contrast to morphine, tramadol has not been shown to cause histamine release. At therapeutic doses, tramadol has no effect on heart rate, left-ventricular function or cardiac index. Orthostatic hypotension has been observed.

PHARMACOKINETICS

ABSORPTION

In a single-dose study, the dose adjusted bioavailability of the 100 mg, 200 mg and 300 mg tablets were equivalent confirming a linear pharmacokinetic response (in relation to both tramadol and O-desmethyltramadol) over this range of strengths. Dose proportionality of the 100 mg, 200 mg and 300 mg tablets has been demonstrated.

Following oral administration of a single dose, tramadol is almost completely absorbed and the absolute bioavailability is approximately 70%. There is no lag time in drug absorption following administration of DUROTRAM[®] XR. DUROTRAM[®] XR exhibits a plasma/time concentration profile with a sharp initial slope similar to immediate-release tramadol capsules followed by a sustained release phase. This behaviour is due to the two phases of drug release which work together to provide a smooth plasma concentration/time profile (Figures 1 and 2).

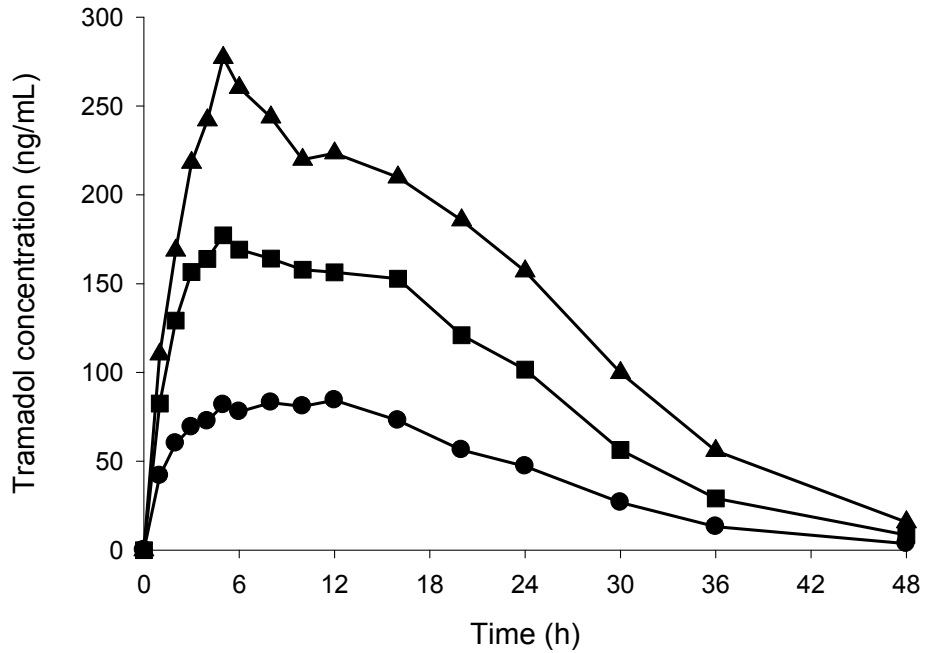


Figure 1. Mean tramadol plasma concentrations following a single oral dose of DUROTRAM XR 100 mg (●), 200 mg (■), 300 mg (▲)

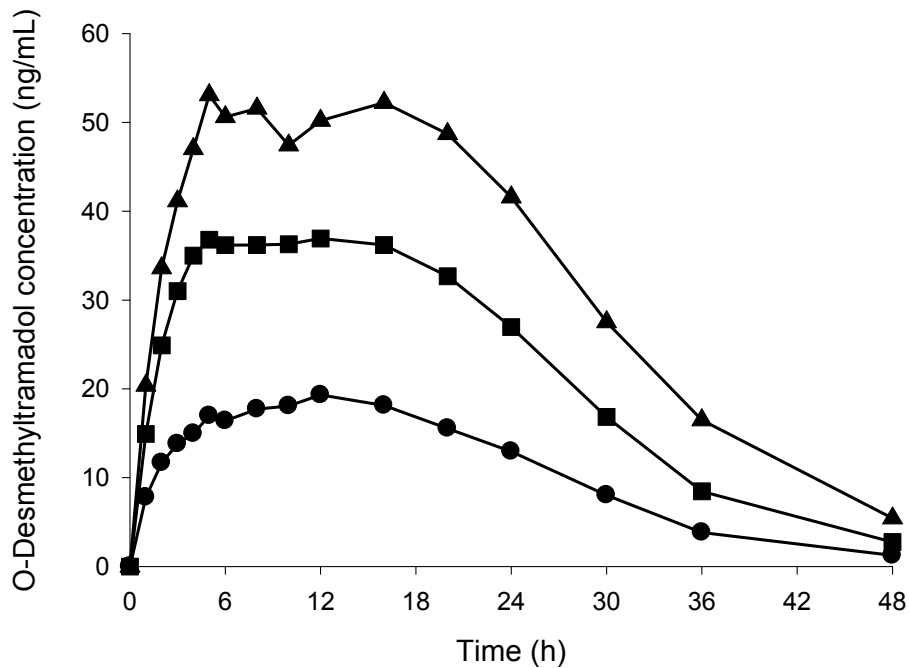


Figure 2. Mean O-desmethyltramadol plasma concentrations following a single oral dose of DUROTRAM XR 100 mg (●), 200 mg (■), 300 mg (▲)

The mean peak steady-state plasma concentrations of tramadol and M1 after multiple dose administration of DUROTRAM[®] XR 200 mg tablets to healthy subjects are attained at about 4.3 h and 7.4 h, respectively (Table 1).

Table 1. Mean (%CV) Steady-State Pharmacokinetic Parameter Values (n=26)

Pharmacokinetic Parameter	Tramadol	M1 Metabolite
	DUROTRAM XR 200 mg Tablet Once-Daily	DUROTRAM XR 200 mg Tablet Once-Daily
AUC ₀₋₂₄ (ng·h/mL)	5185 (28)	1358 (23)
C _{max} (ng/mL)	311 (25)	71 (24)
C _{min} (ng/mL)	107 (49)	35 (23)
T _{max} (hr)*	4.5 (2.0 – 12.0)	5.0 (2.0 – 16.0)
Fluctuation (%)	98 (22)	63 (27)

*T_{max} is presented as Median (Range)

Steady-state plasma concentrations with DUROTRAM[®] XR were reached within 48 hours (Figure 3).

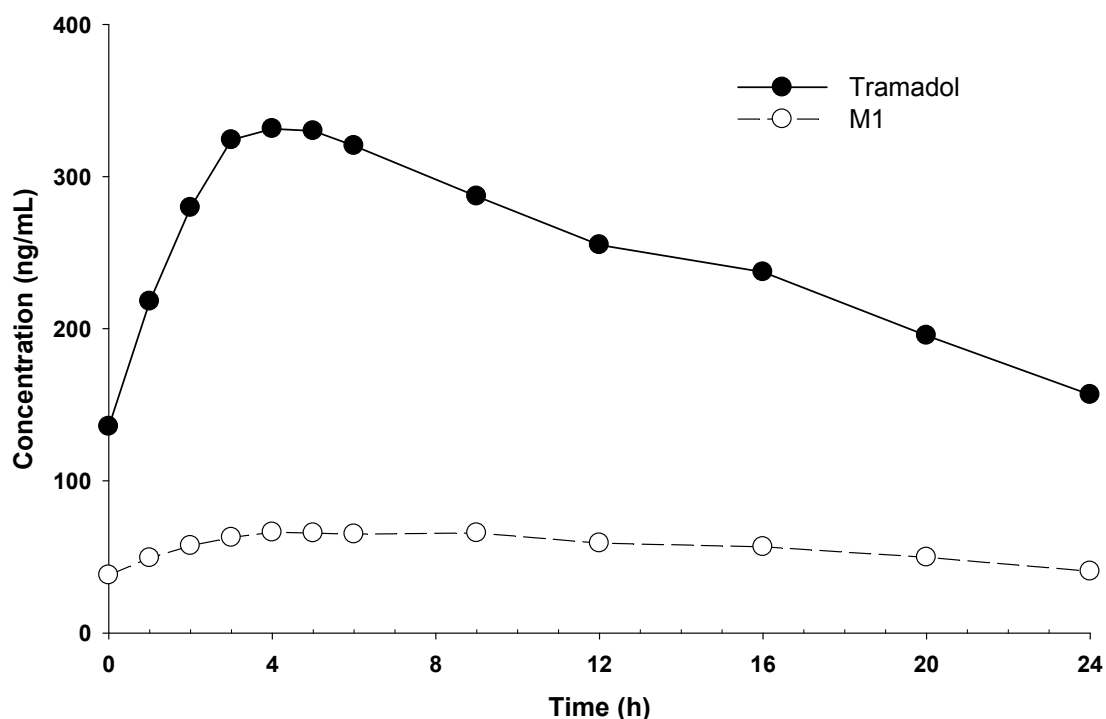


Figure 3. Mean Tramadol Plasma Concentrations at Steady-State Following Oral Administration of Durotram[®] XR 200 mg Once Daily

FOOD EFFECT

The effect of food was investigated in a single dose study in which a DUROTRAM[®] XR 200 mg tablet was given fasting and immediately following a high fat meal. Food had no significant effect on the area under the curve (AUC_{0-∞}) but increased the maximum plasma

concentration (C_{max}) of both tramadol and its metabolite by 54% and 49% respectively. DUROTRAM[®] XR was administered before breakfast in the phase III efficacy and safety clinical trial. (See “CLINICAL TRIALS”.)

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 persons aged over 75 years. The binding of tramadol to human plasma proteins is approximately 20%. Protein binding is independent of concentration up to 10 µg/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range.

METABOLISM

Tramadol is extensively metabolized after oral administration. The major metabolic pathways appear to be N- and O-demethylation and glucuronidation or sulfation in the liver. One metabolite (O-desmethyltramadol, denoted M1) is pharmacologically active in animal models. Formation of M1 is dependent on CYP2D6. Poor CYP2D6 metabolisers may obtain reduced benefit from tramadol due to reduced formation of M1. N-demethylation is catalysed by CYP3A4. The inhibition of one or both of CYP2D6 or CYP3A4 may increase plasma concentrations of tramadol or reduce plasma concentrations of M1.

ELIMINATION

Tramadol and its metabolites are primarily renally excreted, with a cumulative renal excretion of approximately 95%. In young adults, approximately 15-19% of an administered dose is excreted unchanged in the urine, and in the elderly this increases to about 35%. Biliary excretion is of little importance. The total clearance of tramadol is 430-610 mL/min. After single administration of DUROTRAM[®] XR, the mean terminal plasma elimination half-lives of racemic tramadol and racemic M1 are 6.5 ± 1.5 and 7.5 ± 1.4 hours, respectively.

SPECIAL POPULATIONS AND CONDITIONS

RENAL IMPAIRMENT

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. DUROTRAM[®] XR has not been studied in patients with severe renal impairment (creatinine clearance of less than 30 mL/min) and therefore should not be used in these patients. (See CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Renal Impairment and DOSAGE AND ADMINISTRATION.) The total amount of tramadol and M1 removed during a 4-hour dialysis period is less than 7% of the administered dose.

HEPATIC IMPAIRMENT

DUROTRAM[®] XR is contraindicated in patients with severe hepatic impairment. The elimination half-life of tramadol and its active metabolite may be prolonged in patients with hepatic impairment. DUROTRAM[®] XR has not been studied in patients with severe hepatic impairment and, therefore, should not be used. (See CONTRAINDICATIONS, WARNINGS

AND PRECAUTIONS, Hepatic/Biliary/Pancreatic Impairment and DOSAGE AND ADMINISTRATION.)

ELDERLY

Healthy elderly subjects aged 65 to 75 years who are administered an immediate-release formulation of tramadol have plasma concentrations and elimination half-lives comparable to those observed in healthy subjects less than 65 years of age. In subjects aged 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, while the half-life is increased by 15%. The use of DUROTRAM[®] XR is not recommended in patients aged over 75 years. (See DOSAGE AND ADMINISTRATION.)

SEX

Following a 100 mg IV dose of tramadol, plasma clearance was 6.4 mL/min/kg in males and 5.7 mL/min/kg in females. This difference is not likely to be clinically significant; therefore, dosage adjustment based on gender is not recommended.

CHILDREN AND ADOLESCENTS (<18 YEARS)

Pharmacokinetics of DUROTRAM[®] XR tablets have not been studied in paediatric patients below 18 years of age.

CLINICAL TRIALS

In a Phase III, multi-centre, randomised, double-blind, double-dummy, parallel-design study in 431 patients with painful osteoarthritis of the knee, DUROTRAM[®] XR (once daily) was compared with a tramadol twice daily formulation for three months. The dose was titrated to an optimum dose (minimum effective/maximum tolerated dose) within the permitted dose range of 100 mg to 400 mg daily. Inclusion criteria included patients of both sexes aged 40-75 years with osteoarthritis of the knee confirmed in the previous year by arthroscopy or radiology, and an erythrocyte sedimentation rate (ESR) of <40 mm/hour. At baseline, patients were required to have a Western Ontario and McMaster University Osteoarthritis (WOMAC) Index Pain subscale total score of ≥ 150 mm and ≤ 30 minutes morning stiffness with or without crepitus. The WOMAC Index is a self-administered, validated instrument used to assess pain, disability and joint stiffness in knee and hip osteoarthritis. The WOMAC Index Pain subscale total score consists of the sum of the patient's Visual Analogue Scale (VAS) ratings on 5 items relating to the severity of pain. Each response varies from unbearable pain (100 mm) to no pain (0 mm), with the subscale total score being 0-500 mm. The mean \pm SD baseline pain subscale total score for the DUROTRAM[®] XR group was 285 ± 71 and 297 ± 70 for the tramadol twice daily group.

The primary objective of the study was to show non-inferiority of DUROTRAM[®] XR compared with tramadol twice daily on the percentage improvement in the WOMAC Index Pain subscale total score between baseline and day 84. The per-protocol population was used as the primary analysis set to test non-inferiority. The minimal clinically important difference between the two treatments was set at 15%. To conclude that DUROTRAM[®] XR

was not inferior to tramadol twice daily with a 2.5% type I error, the lower bound of the 95% confidence interval (two-sided test) for the mean difference between treatments was required to be greater than -15%. The mean change from baseline to last visit in the WOMAC Index Pain subscale total score was 58%±30% for DUROTRAM® XR and 59%±27% for tramadol twice daily. The 95% confidence interval between the two treatments was -7.6 % to 3.82%. Consequently, as the lower bound interval (-7.6%) was greater than the pre-specified lower bound interval of -15%, DUROTRAM® XR was shown to be non-inferior to tramadol twice daily for the treatment of osteoarthritic knee pain. The median optimum dose in the per-protocol population was 200 mg daily in both treatment groups. The statistical analysis of the primary efficacy outcome in the intention-to-treat population produced similar results. There were a number of secondary efficacy endpoints including WOMAC Stiffness and Physical Function Subscales, patient pain rating at the end of each 24 hour dosing interval (diaries), patient global assessment of pain over 24 hours (VAS) and walking time for 15 metres. The analysis of the secondary endpoints confirmed the similarity of both treatments.

INDICATIONS

Relief of moderate to severe pain.

CONTRAINDICATIONS

- Known hypersensitivity to tramadol or to any of the excipients
- Acute intoxication or overdose with psychotropic medicines
- Acute intoxication or overdose with CNS depressants (alcohol, hypnotics, other opioid analgesics)
- Patients receiving concomitant treatment with MAO inhibitors or who have been treated with MAO inhibitors during the past 2 weeks
- Concomitant treatment with linezolid
- Severe renal or hepatic impairment (creatinine clearance of less than 30 mL/min and/or Child-Pugh Class C)
- Epilepsy not adequately controlled by treatment
- Tramadol must not be administered during breastfeeding if long-term treatment, i.e. more than 2 to 3 days, is necessary.
- Not to be used to treat opioid withdrawal
- Known sensitivity to opioids

PRECAUTIONS

Seizure risk: Seizures have been reported in patients receiving tramadol hydrochloride within the recommended dosage range. Spontaneous postmarketing reports indicate that seizure risk is increased with doses above the recommended range. Concomitant use of tramadol hydrochloride increases the seizure risk in patients taking:

- Selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics),
- Tricyclic antidepressants (TCAs) and other tricyclic compounds or
- Other opioids.

Administration of tramadol may enhance the seizure risk in patients taking:

- MAO inhibitors (see CONTRAINDICATIONS),
- Neuroleptics, or
- Other medicines that lower the seizure threshold (see WARNINGS AND PRECAUTIONS: Interactions with other medicines)

Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections). In tramadol overdose, naloxone administration may increase the risk of seizures.

Patients with controlled epilepsy or patients with a known risk of seizure should only be treated with tramadol in cases of absolute necessity.

Use with alcohol: Consumption of alcohol is not recommended during treatment with tramadol due to the potential for additive effects on central nervous system depression.

Dependency: Tramadol has a low potential for dependence. However, with long-term use, tolerance and psychological and/or physical dependence may develop. At therapeutic doses, withdrawal symptoms have been reported with a frequency of 1 in 8,000 while reports of dependence and abuse have been less frequent.

Because of the potential for dependence or withdrawal to occur, the clinical need for continued analgesia should be reviewed regularly in patients being treated with DUROTRAM[®] XR. In patients with a history of drug abuse or dependence, tramadol should only be used for short periods under strict medical surveillance.

Withdrawal Symptoms: Withdrawal symptoms may occur if DUROTRAM[®] XR is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhoea, upper respiratory symptoms, piloerection and, rarely, hallucinations. Other symptoms that have been seen less frequently with tramadol discontinuation include: panic attacks, severe anxiety and paresthesias.

Clinical experience suggests that signs and symptoms of withdrawal may be avoided by tapering medication when discontinuing tramadol therapy. Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. Clinical experience suggests that withdrawal symptoms may be relieved by reinstatement of tramadol therapy followed by a gradual, tapered dose reduction of the medication combined with symptomatic support.

Tramadol is not suitable as a substitute opioid in opioid-dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms.

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 intraoperative recall. Hence its use during potentially very light planes 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 intraoperative recall. Therefore, if the current practice of administering continuous, potent (volatile or intravenous) anaesthetic agent is followed, tramadol may be used intraoperatively in the same way as other analgesic agents are routinely used.

Intracranial Pressure and Head Trauma: Tramadol should be used with caution in patients with head trauma or increased intra-cranial pressure and in patients who are in shock or in an altered state of consciousness (with no obvious cause).

Anaphylactoid Reactions and Allergic Reactions: Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving therapy with tramadol. When these events occur, it is often following the first dose. Other reported allergic reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis and Stevens-Johnson syndrome. Patients with a history of anaphylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive DUROTRAM[®] XR.

Respiratory Depression: Administer DUROTRAM[®] XR cautiously in patients at risk for respiratory depression, such as patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia or hypercapnia. In these patients, alternative non-opioid analgesics should be considered and opioids should be employed only under careful medical supervision at the lowest effective dose. When large doses of tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures.

Acute abdominal conditions: The administration of DUROTRAM[®] XR may complicate the clinical assessment of patients with acute abdominal conditions.

Renal impairment: DUROTRAM[®] XR is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min, see CONTRAINDICATIONS and PHARMACOKINETICS). Caution is advised in patients with moderate renal impairment.

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. The total amount of tramadol and M1 removed during a 4-hour dialysis period is less than 7% of the administered dose.

Hepatic Impairment: DUROTRAM[®] XR is contraindicated in patients with severe hepatic impairment. (See CONTRAINDICATIONS.) Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver, resulting in both a greater systemic exposure to tramadol and longer tramadol and M1 elimination half-lives (13 hours for tramadol and 19 hours for M1).

Use in the Elderly (> 65 years of age): Dose adjustments in elderly patients up to 75 years of age without clinically relevant hepatic or renal impairment is not normally necessary. However, in patients aged over 75 years, the elimination half-life of tramadol may be prolonged. The use of DUROTRAM[®] XR in patients over the age of 75 years is not recommended. (See PHARMACOKINETICS, DOSAGE AND ADMINISTRATION.)

Use in Children and Adolescents (< 18 years of age): The safety and effectiveness of DUROTRAM[®] XR in children and adolescents less than 18 years of age has not been established. The use of DUROTRAM[®] XR in this age group is not recommended,

Effects on ability to drive and use machines: Tramadol may cause dizziness and/or drowsiness and has, even when used according to the directions, an influence on the ability to drive and use machines. This effect may occur at the beginning of treatment and may be potentiated by alcohol and concomitant use of other CNS-depressants or anti-histamines. If patients are affected they should be warned not to drive or operate machinery.

Carcinogenicity: 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, at doses less than the maximum clinical dose on a body surface basis, but this finding is not believed to suggest risk in humans. No such findings occurred in a rat carcinogenicity study.

Genotoxicity: The weight of evidence from an extensive battery of genotoxicity assays indicates that tramadol does not possess a genotoxic risk to humans.

Effects on Fertility: There were no effects on fertility in rats treated with tramadol at oral doses up to 50 mg/kg/day (approximately the maximum clinical dose on a body surface area basis).

Use in Pregnancy. (Category C): There are no adequate and well controlled studies with tramadol in pregnant women and, therefore, the drug should not be used during pregnancy.

Tramadol has been shown to be embryotoxic and fetotoxic in rats and rabbits at maternotoxic doses (2 to 4 times the maximum clinical dose on a body surface area basis), but there was no evidence of teratogenicity in rats (75 mg/kg/day, or twice the maximum clinical dose on a body surface area basis) or rabbits (175 mg/kg/day, or 8 times the maximum clinical dose on a body surface area basis). There was no fetal harm observed at doses that were not maternotoxic. Embryo and fetal toxicity consisted primarily of reduced fetal weight, skeletal ossification and increased supernumerary ribs. Transient delays in development or behavioural parameters were also seen in pups from rat dams allowed to deliver. Embryo and fetal lethality were reported in only one rabbit study at an extreme maternotoxic dose.

Labour and delivery. Tramadol should not be used in pregnant women prior to or during labour unless the potential benefits outweigh the risks, because safe use in pregnancy has not been established. The use of tramadol during labour may cause neonatal respiratory depression. Tramadol crosses the placenta and, in women during labour, the mean umbilical vein concentration is similar to the maternal vein concentration.

The effects of tramadol on later growth, development and functional maturation of the child are unknown.

Use in Lactation: Tramadol and its metabolites have been detected in human breast milk in small amounts. An infant could ingest 0.1% of the single dose given to their mother. A single administration of tramadol does not usually require breastfeeding to be interrupted. If repeated administration is needed for several days, i.e. more than 2 to 3 days, breastfeeding should be suspended. If long-term treatment after birth is necessary, breastfeeding is contraindicated.

In perinatal and postnatal studies in rats, progeny of dams receiving oral doses of tramadol (1 to 2 times the maximum clinical dose based on body surface area) had reduced weights and pup survival in early lactation. There was no offspring toxicity at lower doses, although maternotoxicity was observed at all dose levels.

Interaction with other Medicines

Overview

In vitro studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated

metabolism of other drugs when it is administered concomitantly at therapeutic doses. 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.

Administration of CYP3A4 inhibitors, such as ketoconazole and erythromycin, or inducers, such as rifampin and St. John's Wort, with DUROTRAM[®] XR may affect the metabolism of tramadol leading to altered tramadol exposure.

Drug-Drug Interactions

MAO Inhibitors

Tramadol is contraindicated in patients receiving MAO inhibitors or who have used them within the previous 14 days. (See CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS.)

Drugs that Lower Seizure Threshold

Tramadol can induce convulsions and increase the potential for selective serotonin reuptake inhibitors (SSRIs), tricyclic anti-depressants (TCAs), anti-psychotics and other seizure threshold lowering drugs to cause convulsions. (See WARNINGS AND PRECAUTIONS.)

CNS Depressants

Concurrent administration of tramadol with other centrally acting drugs, including alcohol, centrally acting analgesics, opioids and psychotropic drugs may potentiate CNS depressant effects.

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 Inhibitors of CYP2D6

In vitro drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, amitriptyline and phenothiazines may inhibit the metabolism of tramadol resulting in increased plasma concentrations.

Use with Quinidine

Tramadol is metabolized to M1 by CYP2D6. As quinidine is a selective inhibitor of that isoenzyme, concomitant administration of quinidine and tramadol results in increased concentrations of tramadol and reduced concentrations of M1. The clinical consequences of these findings are unknown. *In vitro* drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism.

Use with Inhibitors or Inducers of CYP3A4

Administration of CYP3A4 inhibitors, such as ketoconazole and erythromycin, or inducers, such as rifampin and St. John's Wort, may affect the metabolism of tramadol, leading to altered tramadol exposure.

Use with Carbamazepine

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.

Use with Cimetidine

Concomitant administration of tramadol immediate-release capsules with cimetidine does not result in clinically significant changes in tramadol pharmacokinetics. No alteration of the DUROTRAM[®] XR dosage regimen with cimetidine is recommended.

Use with Warfarin-Like Compounds

Post-marketing surveillance of tramadol has revealed rare reports of alteration of warfarin effect, including an increased international normalised ratio (INR).

While such changes have been generally of limited clinical significance for tramadol, periodic evaluation of prothrombin time should be performed when DUROTRAM[®] XR tablets and warfarin-like compounds are administered concurrently.

Use with Serotonergic Agents

The presence of another drug that increases serotonin by any mechanism should alert the treating doctor 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, e.g. selective serotonin reuptake inhibitors (SSRIs). Signs of serotonin syndrome may be, for example, confusion, agitation, fever, sweating, ataxia, hyper-reflexia, 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.

Other Interactions

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

ADVERSE EVENTS

DUROTRAM[®] XR was administered to a total of 215 patients during a clinical study. This was a randomized double-blind parallel-group study of 431 patients with moderate to moderately severe pain due to osteoarthritis of the knee. A titration phase (4 – 12 days) was followed by a maintenance phase (12 weeks). A summary of adverse events occurring at an incidence of 1% or more is given in Table 2, which includes all events, whether considered by the clinical investigator to be related to the study drug or not.

Table 2. Percentage of Patients with Incidence of Adverse Events \geq 1% in 12-week Study MDT3-001/E1

Durotram[®] XR Adverse Events	Total N = 215
Any TEAE	175 (81.4%)
Cardiac disorders	
Angina pectoris	4 (1.9%)
Ear and labyrinth disorders	
Vertigo	5 (2.3%)
Gastrointestinal disorders	
Abdominal pain	3 (1.4%)
Abdominal pain upper	9 (4.2%)
Aptyalism	5 (2.3%)
Constipation	73 (34.0%)
Diarrhoea	5 (2.3%)
Dry mouth	20 (9.3%)
Dyspepsia	3 (1.4%)
Nausea	70 (32.6%)
Vomiting	18 (8.4%)
General disorders and administration site conditions	
Fatigue	9 (4.2%)
Weakness	24 (11.2%)
Immune system disorders	
Hypersensitivity	3 (1.4%)
Metabolism and nutrition disorders	
Anorexia	16 (7.4%)
Musculoskeletal and connective tissue disorders	
Arthralgia	3 (1.4%)
Nervous system disorders	
Dizziness	51 (23.7%)
Dysgeusia	8 (3.7%)
Headache	27 (12.6%)
Somnolence	65 (30.2%)
Psychiatric disorders	
Insomnia	6 (2.8%)
Skin and subcutaneous tissue disorders	
Pruritus	7 (3.3%)
Sweating increased	16 (7.4%)
Vascular disorders	
Hypertension	5 (2.3%)
Hypertension aggravated	4 (1.9%)

The majority (67%) of patients who experienced the most common adverse events ($\geq 1\%$) reported mild to moderate symptoms. Overall, onset of these adverse events usually occurred within the first two weeks of treatment.

Adverse Events with an Incidence of $< 1.0\%$ (whether considered by the clinical investigator to be related to the study drug or not):

Cardiac disorders: extrasystoles, palpitations, coronary artery insufficiency.

Eye disorders: visual acuity reduced, visual disturbance.

Gastrointestinal disorders: abdominal tenderness, duodenal ulcer aggravated, eructation, flatulence, gastric irritation, gastritis, gastritis aggravated, gastroduodenitis, stomach discomfort, toothache.

General disorders and administration site conditions: asthenia, chest pain, lethargy, oedema peripheral, rigors, thirst.

Hepatobiliary disorders: biliary tract disorder, cholecystitis.

Infections and infestations: bronchitis acute, genitourinary tract infection, herpangina, nasopharyngitis, pharyngitis, pyelonephritis chronic, sinusitis acute.

Injury, poisoning and procedural complications: arthropod bite.

Investigations: blood cholesterol abnormal, blood pressure increased, gamma-glutamyltransferase increased, liver function tests abnormal, respiratory rate increased, weight decreased.

Metabolism and nutrition disorders: appetite increased, hypercholesterolemia, hyperuricaemia.

Musculoskeletal and connective tissue disorders: Arthrosis, back pain, muscle cramps, muscle spasms, neck pain, pain in limb.

Nervous system disorders: disturbance in attention, encephalopathy, hypersomnia, hypoaesthesia, hypotonia, ischaemic stroke, parkinsonism aggravated, sciatica, tremor.

Psychiatric disorders: anxiety, crying, dyssomnia, dysthymic disorder, food aversion, libido

decreased, listless, nervousness, neurosis, restlessness, sleep disorder, stress symptoms, tension.

Renal and urinary disorders: bacteriuria, difficulty in micturition, dysuria, nephritis interstitial, leukocyturia.

Reproductive system and breast disorders: breast pain.

Respiratory, thoracic and mediastinal disorders: pharyngolaryngeal pain, rhinitis.

Skin and subcutaneous tissue disorders: photodermatitis, rash.

Vascular disorders: essential hypertension, flushing, hot flushes, thrombophlebitis superficial, vein pain.

Other Adverse Experiences Previously Reported in Clinical Trials or Post-Marketing Reports with Tramadol Hydrochloride

Adverse events which have been reported with the use of tramadol products include convulsions. Other adverse events which have been reported with the use of tramadol products and for which a causal association has not been determined include: difficulty concentrating, hepatitis, liver failure, pulmonary oedema, Stevens-Johnson syndrome and suicidal tendency.

Serotonin syndrome (whose symptoms may include mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures and coma) has been reported with tramadol when used concomitantly with other serotonergic agents such as SSRIs and MAOIs.

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 = $> 1/10$; common = $>1/100$ and $<1/10$; uncommon = $>1/1000$ and $<1/100$; rare = $>1/10,000$ and $<1/1000$; and very rare = $<1/10,000$) were as follows:

Blood and lymphatic system disorders

Uncommon: anaemia, lymphadenopathy, thrombocytopenia

Cardiovascular

Uncommon: orthostatic dysregulation (tendency to collapse and cardiovascular collapse), acute myocardial infarction, angina pectoris, angina unstable, atrial fibrillation,

bradycardia, cardiovascular disorder, palpitations, sinus tachycardia, tachycardia

Ear and labyrinth disorders

Uncommon: cerumen impaction, ear congestion, ear discomfort, ear pain, labyrinthitis, tinnitus

Endocrine disorders

Uncommon: hypothyroidism

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

Eye disorders

Uncommon: cataract, dry eyes, eye pain, eyelid disorder, lacrimation increased, photopsia, scleral haemorrhage, blurred vision

Gastrointestinal

Uncommon: abdominal discomfort, lower abdominal pain, abdominal tenderness, change in bowel habit, constipation aggravated, diverticulitis, dyspepsia aggravated, dysphagia, faecal impaction, faeces discoloured, food poisoning, gastrointestinal haemorrhage, gastrointestinal irritation, gastro-oesophageal reflux disease, hiccups, lip blister, loose stools, pancreatitis aggravated, rectal haemorrhage, rectal prolapse, retching, small intestinal obstruction, urge to vomit

Very rare: elevated liver enzymes

General disorders and administration site conditions

Uncommon: chest tightness, fall, feeling abnormal, feeling cold, inflammation localised, inflammation, influenza like illness, malaise, mass, pain

Hepatobiliary disorders

Uncommon: cholelithiasis

Hypersensitivity and skin

Rare: shock reactions, anaphylaxis

Immune system disorders

Uncommon: hypersensitivity, seasonal allergy

Infections and infestations

Uncommon: abscess limb, bladder infection, bronchitis, ear infection, erysipelas, foot infection fungal, fungal infection, gastroenteritis, gastroenteritis viral, gastrointestinal infection, helicobacter infection, herpes simplex, herpes zoster, laryngitis acute, nail fungal infection, otitis externa, otitis media, otitis media serous, respiratory tract infection viral, sinusitis, stye, tooth abscess, tooth infection, tracheitis, vaginosis fungal, viral infection, wound infection

Injury, poisoning and procedural complications

Uncommon: abrasion, back injury, blister, concussion, eye injury, face injury, hand fracture, head injury, joint sprain, laceration, ligament injury, limb injury, muscle injury, muscle strain, neck injury, postoperative wound complication, soft tissue injury, tendon injury, wrist fracture

Investigations

Uncommon: alanine aminotransferase decreased, alanine aminotransferase increased, aspartate aminotransferase decreased, aspartate aminotransferase increased, blood amylase increased, blood calcium increased, blood cholesterol increased, blood creatinine increased, blood glucose abnormal, blood glucose increased, blood in stool, blood potassium abnormal, blood urea increased, body temperature increased, cardiac murmur, c-reactive protein increased, haematocrit decreased, haematocrit increased, haemoglobin decreased, haemoglobin increased, low density lipoprotein increased, lymphocyte count increased, mammogram abnormal, mean platelet volume decreased, neutrophil count decreased, protein total decreased, red blood cell count decreased, red blood cell count increased, red blood cell sedimentation rate increased, red cell distribution width increased, white blood cell count increased

Metabolism and nutrition disorders

Uncommon: decreased appetite, dehydration, diabetes mellitus, gout, hyperglycaemia, hyperlipidemia, hypertriglyceridaemia, hypocalcaemia, hypokalaemia

Musculoskeletal and connective tissue disorders

Uncommon: back disorder, bone pain, bone spur, bursitis, ganglion, groin pain, joint crepitation, joint disorder, joint stiffness, joint swelling, musculoskeletal discomfort, musculoskeletal stiffness, myalgia, neck pain, neck stiffness, osteoarthritis aggravated, osteopenia, osteoporosis, plantar fasciitis, polyarthralgia, rheumatoid arthritis, temporomandibular joint arthralgia, tendonitis

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Uncommon: benign breast neoplasm, breast cancer invasive, breast cancer, thyroid neoplasm, uterine fibroids

Neurological

Common: sedation

Uncommon: trembling, ataxia, burning sensation, disturbance in attention, dysarthria, dysgeusia, gait abnormal, headache aggravated, hypoaesthesia, mental impairment, migraine, neuralgia, paraesthesia, sinus headache, sleep apnoea syndrome

Rare: changes in mood (usually elevation, occasionally dysphoria) paraesthesia, hallucinations, confusion, coordination disturbance, sleep disturbance, nightmares, 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

Psychiatric disorders

Uncommon: abnormal behaviour, agitation, bipolar disorder, confusion, depression, emotional disturbance, euphoric mood, indifference, irritability

Renal and urinary disorders

Uncommon: calculus renal, haematuria, micturition urgency, nocturia, renal impairment, renal pain, urinary frequency, urinary hesitation, urinary incontinence, urinary retention

Reproductive system and breast disorders

Uncommon: dysmenorrhoea, erectile dysfunction, genital pruritus female, menometrorrhagia, prostatitis, sexual dysfunction, vaginal cyst, vaginal discharge

Respiratory

Uncommon: asthma, chest wall pain, cough, crackles lung, dry throat, dyspnoea, epistaxis, nasal congestion, nasal oedema, productive cough, rhinitis allergic, rhinorrhea, rhonchi, sinus congestion, sinus pain, throat irritation.

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)

Skin and subcutaneous tissue disorders

Uncommon: acne, cold sweat, contusion, dermatitis allergic, dermatitis contact, dermatitis, dermatitis aggravated, dermatosis, dry skin, eczema exacerbated, eczema, erythema, hyperkeratosis, ingrowing nail, night sweat, pallor, piloerection, prurigo, pruritus generalised, rash pruritic, rosacea, skin ulcer, urticaria

Surgical and medical procedures

Uncommon: cardiac pacemaker replacement, colon polypectomy, endodontic procedure, foot operation, hernia repair, lesion excision, tumour excision

Vascular disorders

Uncommon: aortic aneurysm, deep venous thrombosis, haematoma, hot flushes aggravated, hypertension aggravated, hypertension, hypotension, orthostatic hypotension, poor peripheral circulation, vascular insufficiency, wound haemorrhage

Special senses

The incidence of “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 suprathreshold 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 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.

DOSAGE AND ADMINISTRATION

General Advice

DUROTRAM[®] XR tablets must be swallowed whole with liquid and not broken, chewed, dissolved or crushed.

DUROTRAM[®] XR can be taken with or without food. DUROTRAM[®] XR dosage should be individualised according to patient need using the lowest effective dose. The maximum recommended dose of 400 mg once daily should not be exceeded.

Before using DUROTRAM[®] XR for longer than three months, re-assessment of the patient should be undertaken in order to determine whether ongoing treatment is required. If long-term tramadol treatment is required, careful and regular monitoring should be undertaken to establish whether, and to what extent, ongoing treatment with the medicine is necessary.

Alternative tablet strengths of DUROTRAM[®] XR are available. Where necessary, appropriate tablet strengths should be used to achieve the required dose.

Adults

The starting dose is one 100 mg prolonged-release tablet once daily. The usual dose is one 200 mg prolonged-release tablet once daily, to be taken preferably in the evening.

If this does not provide sufficient pain relief, the dosage can be increased in 100 mg dose increments to a maximum of 400 mg once daily.

In general, the lowest effective analgesic dose should be chosen.

DUROTRAM[®] XR should not be used for a period longer than absolutely necessary. If continued pain treatment is necessary due to the nature and severity of the illness, careful regular surveillance should be carried out (including periods without treatment, if necessary) in order to determine the need for continued treatment.

Children and Adolescents (<18 years)

DUROTRAM[®] XR is not recommended for the treatment of children (under 18 years of age). (See also PHARMACOKINETICS and PRECAUTIONS.)

Elderly patients (>65 YEARS)

Dose adjustment in elderly patients (up to 75 years of age) without clinically relevant hepatic or renal impairment is normally not necessary. In patients over 75 years, the elimination half-life of tramadol may be prolonged. The use of DUROTRAM[®] XR in patients over 75 years of age is not recommended. (See also PHARMACOKINETICS and PRECAUTIONS.)

Renal impairment

DUROTRAM[®] XR is contraindicated patients with severe renal impairment (creatinine clearance <30 mL/min). (See also PHARMACOKINETICS, CONTRAINDICATIONS and PRECAUTIONS.)

Hepatic impairment

DUROTRAM[®] XR is contraindicated in patients with severe hepatic impairment. (See also PHARMACOKINETICS, CONTRAINDICATIONS and PRECAUTIONS.)

Missed Dose

If a patient forgets to take one or more doses, they should take their next dose at the normal time and in the normal amount.

OVERDOSAGE

Acute tramadol overdose can result in respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension and death.

Deaths due to overdose have been reported with abuse and misuse of tramadol, by ingesting, inhaling or injecting the crushed tablets. Review of case reports has indicated that the risk of fatal overdose is further increased when tramadol is abused concurrently with alcohol or other CNS depressants, including other opioids.

In the treatment of tramadol overdose, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. General treatment measures should be employed in the management of respiratory failure and/or circulatory shock accompanying overdose.

While naloxone will reverse some, but not all, symptoms caused by overdose with tramadol, the risk of seizures is also increased with naloxone administration. In animals, convulsions following the administration of toxic doses of tramadol could be suppressed with barbiturates or benzodiazepines but were increased with naloxone. Naloxone administration did not change the lethality of an overdose in mice. Hemodialysis is not expected to be helpful in an overdose because it removes less than 7% of the administered dose in a 4-hour dialysis period.

The use of activated charcoal should be considered within the first 1-2 hours after ingestion. As release of tramadol can be sustained following ingestion of DUROTRAM[®] XR, gastric lavage and other procedures to decontaminate the bowel should be considered.

Information on the treatment of overdose should be obtained from the Poisons Information Centre (Phone 13 12 26).

PRESENTATION AND STORAGE CONDITIONS

DUROTRAM[®] XR is available as 100 mg, 200 mg and 300 mg tablets. They are white to off-white, plain, bevelled edge round biconvex tablets. The 100 mg tablets are marked "LP100", the 200 mg tablets are marked "LP200" and the 300 mg tablets are marked "LP300" in black ink.

Supplied in blister packs containing 2*, 3, 5*, 10, 20* and 30* tablets.

* Not currently marketed.

Storage

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE

S4 Prescription Only Medicine

Date of TGA Approval:

1 May 2008