

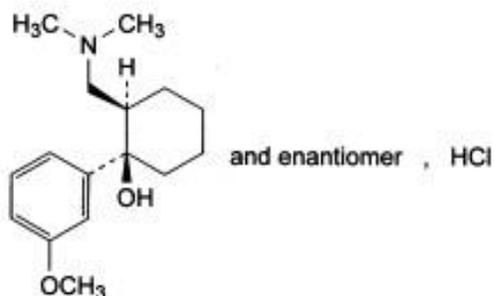
APO-TRAMADOL SR TABLETS

NAME OF THE MEDICINE

Tramadol hydrochloride

Chemical Name: (1*RS*,2*RS*)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride.

Structural Formula:



Molecular formula: $C_{16}H_{25}NO_2 \cdot HCl$

Molecular Weight: 299.84

CAS Registry Number: 53611-16-8

DESCRIPTION

Tramadol hydrochloride is an odourless, white to off white crystalline powder that is readily soluble in both water and ethanol. The water/n-octanol partition coefficient is 1.35 at pH 7.

The excipients contained in each of the three strengths of APO TRAMADOL SR include calcium hydrogen phosphate, hypromellose, colloidal anhydrous silica and magnesium stearate.

PHARMACOLOGY

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 the mode of action is not completely understood, at least two complementary mechanisms appear applicable: binding to mu-opioid receptors and inhibition of reuptake of noradrenaline and serotonin. The opioid-like activity of tramadol derives from low affinity binding of the parent compound to mu-opioid receptors and higher affinity binding of the principal active metabolite, mono O-desmethyltramadol, denoted M1, to mu-opioid receptors. In animal models, M1 is up to six times more potent than tramadol in producing analgesia and 200 times more potent in mu-opioid binding. The contribution of tramadol to human analgesia, relative to M1, is unknown.

Both human and animal 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 reuptake 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 dependent, 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 postoperative analgesia was 300 nanogram/mL, with individual values ranging from 20 to 990 nanogram/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
After oral administration of tramadol modified release tablets, more than 90% of tramadol is absorbed. After a single dose, the mean absolute bioavailability is approximately 70%, irrespective of the concomitant intake of food. Oral bioavailability increases to 90% after repeated administration. The difference between absorbed and bioavailable tramadol is due to first-pass metabolism (maximum 30%).

**Serum tramadol concentrations in young males treated with tramadol SR tablets
(mean ± sd)**

	Single dose		Steady State	
	100 mg	200 mg	100 mg q.12h	200 mg q.12h
Peak (ng/mL)	142 ± 40	260 ± 113	293 ± 113	579 ± 149
Time to peak (h)	4.9 ± 0.8	4.8 ± 0.8	3.5 ± 1.0	3.9 ± 1.1
Trough (ng/mL)	-	-	156 ± 87	265 ± 67

Distribution

Tramadol is rapidly distributed in the body, with a volume of distribution of 2 to 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 microgram/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range.

Tramadol crosses both the placenta and the blood brain barrier. 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 to 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 five to seven hours and the half-life of M1 is six to eight hours. Total clearance is approximately 430 to 610 mL/minute.

Pharmacokinetics in patients with hepatic or renal impairment

Elimination of tramadol and M1 is impaired in patients with hepatic or renal impairment (see **PRECAUTIONS**). In patients with hepatic impairment, the mean half-life of tramadol was found to be 13 hours (range up to 19 hours), and the mean half-life of M1 was 19 hours (range up to 36 hours). In patients with severe renal impairment (creatinine clearance < 5 mL/minute) the mean half-life of tramadol was eleven hours (range up to 20 hours), and the mean half-life of M1 was 17 hours (range up to 43 hours).

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.

CONTRAINDICATIONS

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

Tramadol must not be used for narcotic withdrawal treatment.

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 intraoperative respiratory depression, usually with large

intravenous doses of tramadol and with concurrent administration of respiratory depressants, have been reported.

Increased intracranial pressure, head trauma, shock or reduced levels of consciousness

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.

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 therefore 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 medications that lower the seizure threshold (see **Interactions with other Medicines**). 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.

Intraoperative 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, providing 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.

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 tramadol 150 mg/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.

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. (See Impaired renal function and Impaired hepatic function, below.)

Impaired renal function

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 prolonged-release tablets are not recommended.

As tramadol is only removed very slowly by haemodialysis or haemofiltration, postdialysis administration to maintain analgesia is not usually necessary.

Impaired hepatic function

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 Fertility

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

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 intravenous or intramuscular routes of administration have not been conducted.

Tramadol has been shown to be embryotoxic and fetotoxic in mice, rats and rabbits at 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 fetus 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 fetal toxicity consisted primarily of decreased fetal 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 fetal lethality were reported only in one rabbit study at 300 mg/kg, a dose that would cause extreme maternal toxicity in the rabbit.

In perinatal and postnatal studies in rats, progeny of dams receiving oral (gavage) dose levels of 50 mg/kg had decreased weights and pup survival was decreased early in lactation at 80 mg/kg (six to ten 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.

Category "C": Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

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. If tramadol were to be used during labour, it may cause respiratory depression in the newborn infant. 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 breastfeeding, 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 dose of tramadol 100 mg, the cumulative excretion in breast milk within 16 hours postdose was tramadol 100 microgram (0.1% of the maternal dose) and M1 27 microgram.

Use in Children

The use of tramadol is not recommended as safety and efficacy in children 12 years and under have not been established.

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. Patients 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.

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 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.

Genotoxicity

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 tests in Chinese hamster cells and bone marrow micronucleus tests in mouse and Chinese hamster cells. Weakly mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay and the micronucleus tests in rat cells. Overall, the weight of evidence from these tests indicates tramadol does not possess a genotoxic risk to humans.

Effect on ability to drive or operate machinery

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

INTERACTIONS WITH OTHER MEDICINES

Central nervous system 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, tranquillizers or sedative hypnotics.

The combination of tramadol with mixed opiate agonists/ antagonists (e.g. buprenorphine or 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 doctor to the possibility of an interaction.

Concomitant therapeutic use of tramadol and serotonergic medicines such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see 'Contraindications' section), tricyclic antidepressants and mirtazapine may cause serotonin toxicity. Serotonin syndrome is likely when one of the following is observed:

- Spontaneous clonus

- Inducible or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature >38°C and inducible or ocular clonus

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 (e.g. 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 reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and other seizure threshold lowering drugs (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.

Use with monoamine oxidase inhibitors

Tramadol should not be used in patients who are taking MAOIs or who have taken them within the last 14 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 serum 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 isoenzyme. Drugs that selectively inhibit that isoenzyme (quinidine, phenothiazines and 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, 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 post-operative pain.

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 = > 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:

Immune system disorders

Rare: shock reactions, anaphylaxis, allergic reactions

Endocrine disorders

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

Metabolism and nutrition disorders

Rare: changes in appetite

Psychiatric disorders

Rare: hallucinations, confusional state, sleep disturbance, delirium, anxiety, nightmares, changes in mood (usually euphoric mood, occasionally dysphoria), changes in activity (usually suppression, occasionally increase), changes in cognitive and sensorial capacity (eg. decision behaviour, perception disorders),

Nervous system disorders

Very common: dizziness

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

Uncommon: trembling

Rare: speech disorders, paraesthesia, coordination disturbance, tremor, seizures, involuntary muscle contractions, syncope

Eye disorders

Rare: miosis, mydriasis, visual disturbance (blurred vision)

Cardiac disorders

Uncommon: tachycardia, flushing

Rare: bradycardia

Vascular disorders

Uncommon: orthostatic dysregulation (tendency to collapse and cardiovascular collapse)

Respiratory, thoracic and mediastinal disorders

Rare: dyspnoea, respiratory depression (when the recommended doses are considerably exceeded and other respiratory depressant substances are administered concomitantly)

Very rare: worsening of asthma (causality not established)

Gastrointestinal disorders

Very common: nausea

Common: vomiting, constipation

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

Hepatobiliary disorders:

Very rare: elevated liver enzymes

Skin and subcutaneous tissue disorders

Common: sweating

Uncommon: skin reactions, pruritus, rash

Musculoskeletal and connective tissue disorders:

Rare: motor system weakness

Renal and urinary disorders

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

General disorders and administration site conditions

Common: fatigue

Investigations

Rare: increase in blood pressure

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 mu-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 mu-opioid activity. Delayed mu-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, paraesthesiae, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalisation, derealisation, paranoia).

DOSAGE AND ADMINISTRATION

The dose of tramadol should be titrated according to the severity of the pain and the clinical response of the individual patient. Tramadol is approved for use in adults and adolescents over the age of 12 years.

The recommended dose of Tramadol SR in adults and adolescents over the age of 12 years is 100 to 200 mg twice daily, preferably morning and evening. For initial titration therapy, a lower starting dose may be appropriate for some patients. The tablets are to be taken whole, not divided or chewed, with sufficient liquid, irrespective of food intake. The maximum daily dose should not exceed 400 mg per day.

Paediatric use: The use of Tramadol SR is not recommended as safety and efficacy in children over the age of 12 years have not been established.

Dosage 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 SR prolonged-release tablets are 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. Tramadol is not recommended in patients with severe renal impairment (creatinine clearance < 10 mL/minute).

Hepatic insufficiency: Tramadol SR should not be used in patients with severe hepatic insufficiency.

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 a sustained release oral dose form of tramadol, 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 one to two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration 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. Naloxone did not change the lethality of an overdose in mice.

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

Contact the Poisons Information Centre on 131 126 for advice on the management of overdose.

PRESENTATIONS AND STORAGE CONDITIONS

APO-Tramadol SR 100 mg Tablets Off-white, round, biconvex tablets Blister packs in cartons of 20 tablets AUST R number 154393

APO-Tramadol SR 150 mg Tablets Off-white, capsule-shaped tablets Blister packs in cartons of 20 tablets AUST R number 154394

APO-Tramadol SR 200 mg Tablets Off-white, capsule-shaped tablets Blister packs in cartons of 20 tablets AUST R number 154395

In addition, each tablet contains the following inactive ingredients :

- calcium hydrogen phosphate
- hydroxypropylcellulose
- colloidal anhydrous silica
- magnesium stearate

APO-Tramadol SR Tablets are intended for oral administration. Each modified release (sustained release) tablet contains 100 mg, 150 mg, or 200 mg of tramadol hydrochloride as the active ingredient.

Store below 25°C

NAME AND ADDRESS OF THE SPONSOR

Southern Cross Pharma Pty Ltd 56
Illabunda Drive
Malua Bay, NSW, 2536

NAME AND ADDRESS OF THE DISTRIBUTOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113
Apotex Pty Ltd is the licensee of the registered trade marks APO and APOTEX from the registered proprietor, Apotex Inc.

POISONS SCHEDULE OF THE MEDICINE

S4: Prescription Only Medicine

DATE OF FIRST INCLUSION ON THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (The ARTG): 6th
March 2009

Date of most recent amendment: 14th June 2016