

1. NAME OF THE MEDICINE

Tramadol hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tramadol Mylan SR modified release tablets contain tramadol hydrochloride in the following dose strengths: 100mg, 150mg and 200mg.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Modified release tablets.

Tramadol Mylan SR 100 mg strength: Almost white, round, biconvex, marked with TL 100 on one side.

Tramadol Mylan SR 150 mg strength: Almost white, oval, marked with TL 150 on one side.

Tramadol Mylan SR 200 mg strength: Almost white, oval, marked with TL 200 on one side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Relief of moderate to severe pain.

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dose of Tramadol Mylan SR tablets 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 is not recommended as safety and efficacy in children 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. 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 Mylan SR 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.

Hepatic insufficiency: Tramadol Mylan SR should not be used in patients with severe hepatic insufficiency. In these patients, the immediate release (IR) form of oral tramadol (capsule) may be administered if appropriate. In hepatic impairment, the initial oral dose of tramadol is 50 mg of the immediate release formulation. Depending on the severity of impairment and individual clinical response, the recommended dosage interval for the immediate release may be required to be extended, and/or the dose titrated as required.

4.3 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 receiving MAO (monoamine oxidase) 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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, 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. Physicians 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.

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.

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

section **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION**). 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 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 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.

Note: a parenteral formulation of tramadol is not available.

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.

Use in hepatic impairment

Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver. In cirrhotic patients, dosage reduction is recommended (see section **4.2 DOSE AND METHOD OF ADMINISTRATION**).

Use in renal impairment

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 removed only very slowly by haemodialysis or haemofiltration, post-dialysis administration to maintain analgesia is not usually necessary.

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.

Paediatric use

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

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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, tranquilisers 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. Concomitant therapeutic use of tramadol and serotonergic medicines such as selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see section **4.3 CONTRAINDICATIONS**), 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 re-uptake 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 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 section **4.3 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 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 administration of the anti-emetic 5HT₃ antagonist ondansetron increased the requirements for tramadol in patients with postoperative pain.

4.6 FERTILITY, PREGNANCY AND LACTATION

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 IV or IM routes of administration have not been conducted.

Tramadol has been shown to be embryotoxic and foetotoxic 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 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 had decreased weights and pup survival was decreased early in lactation at 80 mg/kg (6 to 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.

Australian categorisation of Category C. Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus 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. 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 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 100 mg dose of tramadol, the cumulative excretion in breast milk within 16 hours postdose was 100 micrograms of tramadol (0.1% of the maternal dose) and 27 micrograms of M1.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE 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 were as follows (in CIOMS format):

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 $< 1/1000$, Very rare $\leq 1/10,000$.

Psychiatric disorders	
<i>Rare:</i>	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 (e.g. decision behaviour, perception disorders)
Cardiac disorders	
<i>Uncommon:</i>	tachycardia, flushing
<i>Rare:</i>	bradycardia
Vascular disorders	
<i>Uncommon:</i>	orthostatic dysregulation (tendency to collapse and cardiovascular collapse)
Respiratory, thoracic and mediastinal disorders	
<i>Rare:</i>	dyspnoea, respiratory depression (when the recommended doses are considerably exceeded and other respiratory depressant substances are administered concomitantly)
<i>Very Rare</i>	worsening of asthma (causality not established)
Gastrointestinal disorders	
<i>Very common:</i>	nausea
<i>Common:</i>	vomiting, constipation
<i>Uncommon:</i>	dyspepsia, diarrhoea, abdominal pain, flatulence, urge to vomit
Metabolism and nutrition disorders	
<i>Rare:</i>	changes in appetite
Hepatobiliary disorders	
<i>Very rare:</i>	elevated liver enzymes
Nervous system disorders	
<i>Very common:</i>	dizziness
<i>Common:</i>	autonomic nervous effects (mainly dry mouth, perspiration), headache, sedation, asthenia
<i>Uncommon:</i>	trembling
<i>Rare:</i>	speech disorders, paraesthesia, coordination disturbance, tremor, seizures, involuntary muscle contractions, syncope
Endocrine disorders	
<i>Very rare:</i>	syndrome of inappropriate antidiuretic hormone secretion characterized by hyponatraemia secondary to decreased free water excretion
Skin and subcutaneous tissue disorders	
<i>Common:</i>	sweating
<i>Uncommon:</i>	skin reactions, pruritus, rash
Musculoskeletal and connective tissue disorders	
<i>Rare:</i>	motor system weakness
Renal and urinary disorders	
<i>Rare:</i>	micturition disorders (difficulty in passing urine and urinary retention), dysuria
Eye disorders	
<i>Rare:</i>	miosis, mydriasis, visual disturbance (blurred vision)
General disorders and administration site conditions	
<i>Common:</i>	Fatigue
Investigations	
<i>Rare:</i>	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 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, derealisation, paranoia).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <http://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

Few cases of overdose with tramadol have been reported.

Symptoms

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

Treatment

Should overdosage occur, general emergency measures should be implemented. Keep the respiratory airways open, and maintain respiration and circulation. If overdosage is due to ingestion of a sustained release oral dose form such as Tramadol Mylan SR, 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, 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 overdosage 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 overdosage with tramadol with haemodialysis or haemofiltration alone is not suitable for detoxification.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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, mono 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 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 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 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 post-operative 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.

Clinical trials

See section 5.2 PHARMACOKINETIC PROPERTIES, Absorption.

5.2 PHARMACOKINETIC PROPERTIES

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 30 minutes. The absorption half-life ($t_{1/2}$) is 23 ± 11 minutes.

The mean peak tramadol 50 mg capsule serum level (C_{max}) is reached 1 hour (range 1 to 4 hours) after administration. The mean peak plasma concentration (C_{max}) is approximately 360 nanogram/mL after oral administration of two tramadol 50 mg capsules.

In another study, after oral administration of two 50 mg capsules, the mean absolute bioavailability (f_{abs}) is 68 to 72%. 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.

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.

More than 90% of tramadol is absorbed after oral administration of tramadol hydrochloride modified release tablets. 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%).

The administration of tramadol hydrochloride modified release tablets every 12 hours and tramadol hydrochloride immediate release tablets every 6 hours at the same total daily dose, resulted in similar peak and trough serum tramadol concentrations and total tramadol exposure for the two preparations.

Serum tramadol concentrations in young males treated with tramadol hydrochloride modified release tablets (mean ± sd)			
	Single Dose 100 mg¹	Single Dose 200 mg²	Steady State 200 mg every 12 hours³
C _{max} (ng/mL)	195.8 ± 48.8	363.7 ± 85.8	491.9 ± 119.1
T _{max} (h)	4.36 ± 1.09	4.71 ± 1.34	4.04 ± 1.10
AUC _{0-∞} (ng.hr/mL)	3058.6 ± 1221.8	6117.1 ± 1747.5	-
AUC _{0-t} (ng.hr/mL)	2974.0 ± 1143.4	5729.9 ± 1570.5	6508.9 ± 1915.1
C _{min} (ng/mL)	-	-	106.3 ± 56.0

¹ Initiated in a study consisting of a single dose of 100mg tramadol at time zero under fasting conditions, consisting of 24 healthy male and female volunteers (Study ZPS- 342).

² Initiated in a study consisting of a single dose of 200mg tramadol at time zero under fasting conditions, consisting of 23 healthy male and female volunteers (Study ZPS-277).

³ Initiated in a study consisting of a single dose of 200mg tramadol at time zero under fasting conditions and at steady state, consisting of 24 healthy male and female volunteers (Study ZPS-332).

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 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 mean half-life of tramadol is 7-8 hours and the half-life of M1 is 8-9 hours. Total clearance is approximately 430 to 610 mL/min.

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 including subjects with a considerably decreased CL_{Cr} (creatinine clearance <5 mL/min) the mean half-life of tramadol was 11 hours (range up to 20 hours), and the mean half-life of M1 was 17 hours (range up to 43 hours).

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%).

5.3 PRECLINICAL SAFETY DATA

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 test 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.

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.

6. PHARMACEUTICAL PROPERTIES

6.1 LIST OF EXCIPIENTS

Tramadol Mylan SR modified release tablets, available in 100 mg, 150 mg and 200 mg strengths, contain the following inactive ingredients: glyceryl behenate, calcium hydrogen phosphate dihydrate, povidone and colloidal anhydrous silica.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Tramadol Mylan SR modified release tablets are blister packed and available in strengths of 100 mg, 150 mg and 200 mg tramadol.

All strengths are available in PVC/AL blister packs of 20 or 60 modified release tablets.

Not all presentations are marketed in Australia.

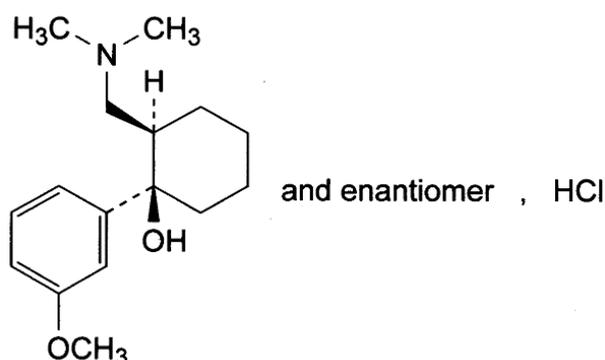
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

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 analgesics class and has an opioid-like activity.

Chemical structure:



CAS#: 36282-47-0

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8. SPONSOR

Alphapharm Pty Limited / Mylan Health Pty Ltd

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

ABN 93 002 359 739

www.mylan.com.au

9. DATE OF FIRST APPROVAL

14/02/2008

10. DATE OF REVISION

22 May 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of New Information

Tramadol Mylan SR_pi\May18/00