

New Zealand Data Sheet

Tramal[®] Capsules Tramal[®] Solution for Injection Tramal[®] SR Tablets Tramal[®] Oral Drops

1. PRODUCT NAME

Tramal[®] (tramadol hydrochloride) immediate release capsules 50 mg
Tramal[®] (tramadol hydrochloride) solution for injection 50 mg/mL, 100 mg/2mL
Tramal[®] SR tablets (tramadol hydrochloride) sustained release tablets) 50 mg, 100 mg, 150 mg, 200 mg
Tramal[®] oral drops (tramadol hydrochloride) immediate release, solution 100 mg/mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

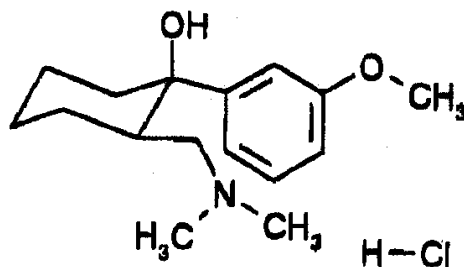
Tramal[®] 50 mg capsules are yellow-yellow capsules containing: 50 mg tramadol hydrochloride.

Tramal[®] 50 mg and 100 mg injections contain: tramadol hydrochloride 50mg/mL.
Tramal[®] SR sustained release tablets contain: tramadol hydrochloride in the following dose strengths: 50, 100, 150 and 200 mg.

Tramal[®] oral drops 100 mg/mL contain: tramadol hydrochloride 100 mg/mL.
For full list of excipients, see section 6.1

Tramal[®] capsules, Tramal[®] solution for injection, Tramal[®] SR tablets and Tramal[®] oral drops contain tramadol hydrochloride which is (±) - *cis*-2-(dimethylaminomethyl)-1-(3-methoxyphenyl)-cyclohexanol hydrochloride. Tramadol hydrochloride is an odourless, white to off-white crystalline powder that is readily soluble in both water and ethanol and has a pKa of 9.41. The water/n-octanol partition coefficient is 1.35 at pH 7. It belongs to the synthetic analgesics class and has opioid-like activity, with the formula: C₁₆ H₂₅ NO₂. HCl. MW = 299.84.

The structural formula of tramadol hydrochloride is:-



The CAS Registry Number is 36282-47-0.

3. PHARMACEUTICAL FORM

Tramal[®] capsules are oblong, yellow/yellow, shiny hard gelatine capsules size 4.

Tramal[®] solution for injection is clear, colourless solution.

Tramal[®] oral drops, solution are available in bottle with dropper device or bottle with metered dose pump.

Tramal[®] SR 50mg sustained release tablets are pale yellow coloured, round, biconvex, film-coated tablets, engraved with "T0" on one side and Grunenthal logo on the other side.

Tramal[®] SR 100 mg sustained release tablets are supplied as white, round, biconvex, film-coated tablets, engraved with "T1" on one side and the Grunenthal logo on the other side.

Tramal[®] SR 150 mg sustained release tablets are supplied as pale orange-coloured, round, bi-convex, film-coated tablets, engraved with "T2" on one side and the Grunenthal logo on the other side.

Tramal[®] SR 200 mg sustained release tablets are supplied as slightly brownish orange-coloured, round, bi-convex, film-coated tablets, engraved with "T3" on one side and the Grunenthal logo on the other side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Relief of moderate to severe pain.

4.2 Dose and method of administration

Dose

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

The recommended dosage of Tramal[®] capsules, Tramal[®] solution for injection, Tramal[®] SR tablets and Tramal[®] oral drops respectively are as follows:

Tramal[®] capsules

Oral administration - for the treatment of moderate pain Tramal[®] 50 – 100 mg administered two or three times daily may be sufficient. Tramal[®] 50 mg may be adequate as the initial dose for moderate pain.

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

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

Tramal® solution for injection

Parenteral administration - Tramal® injection may be administered by intravenous injection by intravenous or intramuscular injection. Few data are available on the administration of Tramal® by repeated intramuscular injection. Intravenous injections should be given slowly over 2-3 minutes.

For postoperative pain, an initial bolus of 100 mg should be administered. Subsequent doses of 50mg or 100mg every four to six hours may be given, up to a total daily dose of 600 mg.

For less severe pain, 50 mg or 100 mg every four to six hours to a maximum of 400 mg per day.

PHARMACEUTICAL PRECAUTIONS

Tramal® solution for injection is incompatible with injection solutions containing diclofenac, indomethacin, phenylbutazone, diazepam, flunitrazepam, glyceryl trinitrate or midazolam. Tramal® solution for injection is compatible with the following intravenous fluids: 0.9% sodium chloride, 5% glucose, 4.2% sodium bicarbonate, Ringer's solution, Ringer's lactate solution, Dextran 40 (10%) or polygeline 3.5%.

Tramal® SR tablets

Oral administration - the recommended dose of Tramal® SR in adults and adolescents over the age of 12 years is 100 mg 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.

Tramal® oral drops, solution with dropper device

Oral administration - for moderate pain, the recommended dose of Tramal® oral drops in adults and adolescents over the age of 12 years is a single dose of 20 drops of Tramal® oral drops. This provides 50 mg of tramadol hydrochloride. If there is no pain relief after 30 to 60 minutes, a second dose of 20 drops of Tramal® oral drops can be taken. Depending on the pain, the analgesic effect lasts for 4 to 6 hours.

For severe pain, the recommended dose of Tramal® oral drops in adults and adolescents over the age of 12 years is a single dose of 40 drops of Tramal® oral drops. This provides 100 mg of tramadol hydrochloride.

The maximum daily dose should not exceed a total of 160 drops (that is 8 x 20 drops or 4 x 40 drops). This maximum daily dose provides 400 mg tramadol hydrochloride.

If more than 7 days have elapsed since the pump has been used, it is essential to re-prime the pump for accurate dispensing by pressing the nozzle 5 times immediately prior to use.

Contents of tramadol hydrochloride in single drops:

Drop number	Tramadol hydrochloride
1 drop	2.5 mg
5 drops	12.5 mg
10 drops	25 mg

15 drops	37.5 mg
20 drops	50 mg
25 drops	62.5 mg
30 drops	75 mg
35 drops	87.5 mg
40 drops	100 mg

Tramal® oral drops, solution with dosage pump

Oral administration - for moderate pain, the recommended dose of Tramal® oral drops in adults and adolescents over the age of 12 years is a single dose of 4 pumps (1 press of nozzle = 1 pump) of Tramal® oral drops. This provides 50 mg of tramadol hydrochloride. If there is no pain relief after 30 to 60 minutes, a second dose of 4 pumps of Tramal® oral drops can be taken. Depending on the pain, the analgesic effect lasts for 4 to 6 hours.

For severe pain, the recommended dose of Tramal® oral drops in adults and adolescents over the age of 12 years is a single dose of 8 pumps of Tramal® oral drops. This provides 100 mg of tramadol hydrochloride.

The maximum daily dose should not exceed a total of 32 pumps. This maximum daily dose provides 400 mg tramadol hydrochloride.

Solution in bottle with metered dose pump:

Tramal oral drops, solution is supplied as either dropper container or bottle with metering pump. Please be aware that 1 press of the metering pump does not correspond to 1 drop from the dropper device. See the table below for further details:

Full presses of the pump	Tramadol hydrochloride	Equivalent number of drops
1 press	12.5 mg	5 drops
2 presses	25 mg	10 drops
3 presses	37.5 mg	15 drops
4 presses	50 mg	20 drops
5 presses	62.5 mg	25 drops
6 presses	75 mg	30 drops
7 presses	87.5 mg	35 drops
8 presses	100 mg	40 drops

Paediatric use - Tramal® solution for injection and Tramal® oral drops are approved for use in children 2 years old and over. On account of their high dosage strengths, capsules and SR tablets are not recommended for use in children below the age of 12 years. Analgesic dosage of Tramal® solution for injection and Tramal® oral drops must be individualised by the physician according to the severity of pain as well as on the basis of patient's age and weight. The recommended dose of Tramal® solution for injection and Tramal® oral drops in children between the ages of 2 and 12 is 1-2mg/kg **up to a maximum daily dose of the lesser of 8 mg/kg/day or 400 mg/day.**

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 Tramal 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.

Hepatic insufficiency - Tramal® 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 the impairment and individual clinical response, the recommended dosage interval (4-6 hours) may require to be extended, and/or the dose level titrated as required.

Method of administration

For method of administration see section **4.2 Dose**

4.3 Contraindications

Tramadol is contraindicated in:

- individuals with known hypersensitivity to tramadol or any excipients listed in section 6.1
- acute intoxication with alcohol, hypnotics, analgesics, opioids or psychotropic drugs
- patients who are taking MAO inhibitors or who have taken them within the last 14 days
- known hypersensitivity to opioids
- patients with uncontrolled epilepsy or epilepsy not adequately controlled by treatment.

Tramadol must not be used for narcotic withdrawal treatment.

4.4 Special warnings and precautions for use

Galactose intolerance

Tramal® SR tablets contain 2.5 mg lactose monohydrate per tablet. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should consult a physician before use.

Acute abdominal conditions

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

Respiratory depression and sedation

Tramadol should be administered cautiously in patients at risk of respiratory depression.

Cases of intra-operative respiratory depression, usually with large intravenous doses of tramadol and with concurrent administration of respiratory depressants, have been reported.

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of tramadol with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine, sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, medicines with antihistamine-sedating actions such as antipsychotics, other opioids and alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of medicine-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [see **Section 4.5 Interactions with other medicines and other forms of interaction**].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a

lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when tramadol is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs [see **Section 4.5 Interactions with other medicines and other forms of interaction**].

Increased intracranial pressure or 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.

Renal and hepatic disease

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

Renal disease

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

Hepatic disease

Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver. In cirrhotic patients, dosage reduction is recommended (see **4.2 Dose and method of administration**).

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 **4.5 Interaction 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.

Paediatric use

Tramal[®] solution for injection and Tramal[®] oral drops are approved for use in children 2 years old and over. On account of their high dosage strengths, capsules and SR tablets are not recommended for use in children below the age of 12 years (see **4.2 Dose and method of administration**).

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.

Intra-operative use

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

Long-term use

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

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

4.5 Interaction with other medicines and other forms of interaction

Use with Benzodiazepines and other Central Nervous System (CNS) Depressants - due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required.

Follow patients closely for signs of respiratory depression and sedation [see **Section 4.4 Warnings and Precautions**].

Tramadol should be used with caution and in reduced dosages when administered to patients receiving Benzodiazepines and CNS depressants such as sedative/hypnotics, anxiolytics, tranquillisers, muscle relaxants, general anaesthetics, drugs with antihistamine-sedating actions such as antipsychotics, phenothiazines, alcohol, other opioids.

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 **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 $>38^{\circ}\text{C}$ 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 (eg. warfarin) due to reports of increased international normalised ratio (INR) with major bleeding and ecchymoses in some patients.

Drugs which reduce the seizure threshold - tramadol can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors(SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and other seizure threshold lowering agents (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 **4.3 Contraindications**).

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

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

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

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

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

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

4.6 Fertility, pregnancy and lactation

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

Use in pregnancy - Category C

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

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

Labour and delivery

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

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

Use in lactation

Tramadol is not recommended during breast feeding, because its safety in infants and newborns has not been studied. Low levels of tramadol have been detected in breast milk. Following a single intravenous 100 mg dose of tramadol, the cumulative excretion in breast

milk within 16 hours post-dose was 100 µg of tramadol (0.1% of the maternal dose) and 27 µg of M1.

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 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 (in CIOMS format where very common $\geq 1/10$; common $\geq 1/100$ and $< 1/10$; uncommon $\geq 1/1000$ and $< 1/100$; rare $\geq 1/10,000$ and $< 1/1000$; and very rare $\leq 1/10,000$) were as follows:

Cardiac disorders

Uncommon: tachycardia, flushing

Rare: bradycardia

Investigations

Rare: increase in blood pressure

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

Metabolism and nutrition disorders

Rare: changes in appetite

Hepatobiliary disorders:

Very rare: elevated liver enzymes

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

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)

Musculoskeletal and connective tissue disorders

Rare: motor system weakness

General disorders and administration site conditions:

Common: fatigue

Endocrine

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

Skin and subcutaneous tissue disorders

Common: sweating

Uncommon: skin reactions, pruritus, rash

Immune system disorders

Rare: shock reactions, anaphylaxis, allergic reactions

Renal and urinary disorders

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

Eye disorders

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

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

Drug abuse and dependence

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

Tolerance and withdrawal

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare

professionals are asked to report any suspected adverse reactions
<https://nzphvc.otago.ac.nz/reporting/>

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 analgesics (opioids) 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 an oral dose form, emptying the stomach by gastric lavage should be considered because of the possibility of ongoing release in the stomach.

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

Naloxone will reverse respiratory depression, but not all symptoms caused by 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 advise on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766)

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other opioids

ATC Code: N02AX02

Tramadol is a centrally-acting synthetic analgesic of the aminocyclohexanol group with opioid-like effects. It is not derived from natural sources, nor is it chemically related to opiates. Although pre-clinical testing has not completely explained the mode of action, at least two complementary mechanisms appear applicable: binding to μ -opioid receptors and inhibition of re-uptake of noradrenaline and serotonin. The opioid-like activity of tramadol derives from low affinity binding of the parent compound to μ -opioid receptors and higher affinity binding of the principal active metabolite, O-desmethyltramadol, denoted M1, to μ -opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ -opioid binding. The contribution to human analgesia of tramadol relative to M1 is unknown.

Both animal and human studies have shown that antinociception induced by tramadol is only partially antagonised by the opiate antagonist naloxone. In addition, tramadol has been

shown to inhibit re-uptake of noradrenaline and serotonin *in vitro*, as have some other opioid analgesics. These latter mechanisms may contribute independently to the overall analgesic profile of tramadol.

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

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

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

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

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

After intramuscular injection of 50mg tramadol, the bioavailability is approximately 100%, and the peak serum level is attained after 45 minutes (range 15 to 90).

After oral administration of Tramal[®] SR, 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 of 30%). The administration of Tramal[®] SR every 12 hours and Tramal[®] (immediate release) every 6 hours at the same 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 Tramal® SR (mean ± sd)

	Single Dose		Steady State	
	100 mg	200 mg	100 mg q12 h	200 mg q12 h
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	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 – 3 L/kg in young adults. The volume of distribution is reduced by about 25% in those aged over 75 years. Plasma protein binding is about 20% and is independent of concentration up to 10 µg/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range.

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

Metabolism

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

Excretion

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

Pharmacokinetics in patients with hepatic or renal impairment

Elimination of tramadol and M1 is impaired in patients with hepatic or renal impairment (see **4.4 Special warnings and precautions for use**). In patients with hepatic impairment, the mean half-life of tramadol was found to be 13 h (range up to 19 h), and the mean half-life of M1 was 19 h (range up to 36 h). In patients with renal impairment including subjects with considerably decreased CL_{Cr} [$< 5\text{ mL/min}$] the mean half-life of tramadol was 11 h (range up to 20 h), and the mean half life of M1 was 17 h (range up to 43 h).

Pharmacokinetics in the elderly

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

5.3 Preclinical safety data

Carcinogenesis, mutagenesis and impairment of fertility

Tramadol was not mutagenic in the following assays: Ames *Salmonella* microsomal activation test, CHO/HPRT mammalian cell assay, mouse lymphoma assay (in the presence of metabolic activation), dominant lethal mutation tests in mice, chromosome aberration test in Chinese hamster cells, and bone marrow micronucleus tests in mice and Chinese hamster cells. Weakly mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay and micronucleus tests in rat cells. Overall, the weight of evidence from these tests indicates tramadol does not possess a genotoxic risk to humans.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tramal® 50 mg capsules:

Excipients include: cellulose-microcrystalline, magnesium stearate, sodium starch glycollate, silica-colloidal anhydrous. Excipients in the capsule shell are: iron oxide yellow (CI 77492), titanium dioxide (CI 173015), sodium lauryl sulphate and gelatine.

Tramal® 50 mg and 100 mg injections:

Excipients are: sodium acetate, Water for Injections.

Tramal® SR sustained release tablets:

Excipients are: hypromellose¹⁰ mPa.s, silica-colloidal anhydrous, magnesium stearate, microcrystalline cellulose. Excipients in the film coat are: hypromellose 6 mPa.s, lactose monohydrate, macrogol 6000, propylene glycol, purified talc, titanium dioxide, quinoline yellow aluminium lake CI 47005 (150 and 200 mg tablets only), iron oxide red CI 77491 (150 and 200 mg tablets only), iron oxide yellow CI 77492 (50 and 200 mg tablets only) and iron oxide black CI 77499 (200 mg tablet only).

Tramal® oral drops 100 mg/mL:

The excipients in the oral drops include potassium sorbate, glycerol, propylene glycol, sucrose, sodium cyclamate, saccharin sodium, ethoxylated hydrogenated castor oil, mint oil (partly dementholised), aniseed flavour (87122), and purified water.

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

Tramal® capsules have a shelf-life of 36 months when stored below 30°C.

Tramal® solution for injection and Tramal®SR 100, 150 and 200 mg tablets have a shelf-life of 60 months when stored below 30°C.

Tramal[®] SR 50 mg tablets have a shelf life of 36 months when stored below 30°C.

Tramal[®] oral drops have a shelf-life of 36 months when stored below 30°C. Protect from light

6.4 Special precaution for storage

For storage conditions of the medicine, see section 6.3

6.5 Nature and contents of container

Tramal[®] 50mg immediate release capsules-packs of 6, 10, 20, 30 and 50 capsules.

Tramal[®] 50, solution for injection-pack containing 5 ampoules of 1 mL each.

Tramal[®] 100, solution for injection-pack containing 5 ampoules of 2 mL each.

Tramal[®] SR 50 mg, 100 mg, 150 mg and 200 mg sustained release tablets - packs of 20 and 60 tablets.

Tramal[®] oral drops, solution presented in the following bottle sizes: 10 mL with dropper device, 30 mL, 50 mL and 100 mL with dosage pump.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Tramal[®] capsules

If your doctor tells you to stop taking TRAMAL[®] capsules or it passes its expiry date, ask your pharmacist what to do with any TRAMAL[®] capsules that are left over.

Tramal[®] solution for injection

If your doctor tells you to stop taking TRAMAL[®] or it passes its expiry date, ask your pharmacist what to do with any TRAMAL[®] that is left over.

Tramal[®] oral drops

If the packaging is damaged, return it to your pharmacist for disposal.

If your doctor tells you to stop taking this medicine or the expiry date has passed, ask your pharmacist what to do with any Tramal[®] oral drops that is left over.

Tramal[®] SR tablets

If your doctor tells you to stop taking this medicine or the expiry date has passed, ask your pharmacist what to do with any Tramal[®] SR that is left over.

7. MEDICINE SCHEDULE

Prescription-only Medicine

8. SPONSOR

Seqirus (NZ) Ltd
PO Box 62 590
Greenlane, Auckland 1546
New Zealand
Telephone: 0800 502 757

9. DATE OF FIRST APPROVAL

Tramal[®] capsules – 25/9/1997
Tramal[®] solution for injection – 25/9/1997
Tramal[®] oral drops – 29/9/2005
Tramal[®] SR 50mg – 2/11/2006
Tramal[®] SR 100 mg – 2/3/2000
Tramal[®] SR 150mg – 2/3/2000
Tramal[®] SR 200 mg – 2/3/2000

10. DATE OF REVISION OF THE TEXT

8 May 2017

Tramal[®] is a registered trademark of Grunenthal GmbH used by Seqirus as authorised user.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Data sheet reformatted as per Data Sheet Explanatory Guide v1.0 March 2017
8	Change in sponsor name
4.4	Excipient lactose is replaced with Australian Approved name 'lactose monohydrate' for consistency with Australian PI
6	Excipient lactose is replaced with Australian Approved name 'lactose monohydrate' for consistency with Australian PI
4.4	As per Medsafe proposal, Warning and Precautions are updated to include information on 'tramadol' and 'Respiratory depression and sedation'.
4.5	As per Medsafe proposal, information on Interaction between 'tramadol' and 'Benzodiazepines and other CNS depressants' is updated