AUSTRALIAN PRODUCT INFORMATION

TRAMEDO® SR (TRAMADOL HYDROCHLORIDE) MODIFIED RELEASE TABLETS

WARNINGS

Limitations of use

Because of the risks associated with the use of opioids, TRAMEDO SR should only be used in patients for whom other treatment options, including non-opioid analgesics, are ineffective, not tolerated or otherwise inadequate to provide appropriate management of pain (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Hazardous and harmful use

TRAMEDO SR poses risks of hazardous and harmful use which can lead to overdose and death. Assess the patient's risk of hazardous and harmful use before prescribing and monitor the patient regularly during treatment (see section 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Life threatening respiratory depression

Serious, life-threatening or fatal respiratory depression may occur with the use of TRAMEDO SR. Be aware of situations which increase the risk of respiratory depression, modify dosing in patients at risk and monitor patients closely, especially on initiation or following a dose increase (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Concomitant use of benzodiazepines and other central nervous system (CNS) depressants, including alcohol

Concomitant use of opioids with benzodiazepines, gabapentinoids, antihistamines, tricyclic antidepressants, antipsychotics, cannabis or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required; and monitor patients for signs and symptoms of respiratory depression and sedation. Caution patients not to drink alcohol while taking TRAMEDO SR.

1 NAME OF THE MEDICINE

Tramadol hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TRAMEDO SR tablets contain the active ingredient tramadol hydrochloride.

Each modified release (sustained release) tablet contains 100 mg, 150 mg, or 200 mg of tramadol hydrochloride as the active ingredient.

For the full list of excipients, see section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

TRAMEDO SR modified release tablets are available in the three (3) strengths as follows:

- 100 mg - Off-white, round, biconvex tablets plain on both sides
- 150 mg - Off-white, capsule-shaped tablets plain on both sides
- 200 mg - Off-white, capsule-shaped tablets plain on both sides

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TRAMEDO SR is indicated for the management of severe pain where:

- other treatment options have failed, are contraindicated, not tolerated or are otherwise inappropriate to provide sufficient management of pain, and
- the pain is opioid-responsive, and
- requires daily, continuous, long-term treatment.

TRAMEDO SR is not indicated for use in chronic non-cancer pain other than in exceptional circumstances.

TRAMEDO SR is not indicated as an as-needed (PRN) analgesia.

4.2 DOSE AND METHOD OF 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.

TRAMEDO SR is contraindicated in all children younger than 12 years of age and in postoperative management of children younger than 18 years of age following tonsillectomy and/or adenoidectomy (see section 4.3 – CONTRAINDICATIONS and section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Paediatric use).

TRAMEDO SR tablets: The recommended dose of TRAMEDO 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.

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 TRAMEDO SR modified 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 (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Tramadol is not recommended in patients with severe renal impairment (creatinine clearance < 10 mL/minute).

Hepatic insufficiency: TRAMEDO SR should not be used in patients with severe hepatic insufficiency (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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;
- severe respiratory disease, acute respiratory disease and respiratory depression;
- all children younger than 12 years of age (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS)
- postoperative management of children younger than 18 years of age following tonsillectomy and/or adenoidectomy (see section 4.4 - SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
- 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hazardous and harmful use

TRAMEDO SR contains the opioid tramadol hydrochloride and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed TRAMEDO SR at recommended doses.

The risk of addiction is increased in patients with a personal or family history of substance abuse (including alcohol and prescription and illicit drugs) or mental illness. The risk also increases the longer the drug is used and with higher doses. Patients should be assessed for their risks for opioid abuse or addiction prior to being prescribed TRAMEDO SR.

All patients receiving opioids should be routinely monitored for signs of misuse and abuse. Opioids are sought by people with addiction and may be subject to diversion. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the safe storage and proper disposal of any unused drug (see section 6.4 SPECIAL PRECAUTIONS FOR STORAGE and section 6.6 SPECIAL PECAUTIONS FOR DISPOSAL). Caution patients that abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.

PATIENTS SHOULD BE ADVISED NOT TO SHARE TRAMEDO SR WITH ANYONE ELSE.

Respiratory depression

Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of TRAMEDO SR but the risk is greatest during initiation of therapy or following an increase in dose. Patients should be monitored closely for respiratory depression at these times.

The risk of life-threatening respiratory depression is also higher in elderly, frail, or debilitated patients and in patients with existing impairment of respiratory function (e.g. chronic obstructive pulmonary disease; asthma) hepatic or renal impairment (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Opioids should be used with caution and with close monitoring in these patients (see section 4.2 DOSE AND METHOD OF ADMINISTRATION). The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see section 4.3 CONTRAINDICATIONS).

The risk of respiratory depression is greater with the use of high doses of opioids, especially high potency and modified release formulations, and in opioid naïve patients. Initiation of opioid treatment should be at the lower end of the dosage recommendations with careful titration of doses to achieve effective pain relief. Careful calculation of equianalgesic doses is required when changing opioids or switching from immediate release to modified release formulations, (see section 4.2 DOSE AND METHOD OF ADMINISTRATION), together with consideration of pharmacological differences between opioids. Consider starting the new opioid at a reduced dose to account for individual variation in response.

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.

Sleep-related breathing disorders

Drugs with mu-opioid receptor agonist activity, such as tramadol, can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Use of these drugs increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol

Concomitant use of opioids and benzodiazepines or other CNS depressants, including alcohol, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of TRAMEDO SR with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics and other CNS depressants, should be reserved for patients for whom other treatment options are not possible.

If a decision is made to prescribe TRAMEDO SR concomitantly with any of the medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. Patients should be followed closely for signs and symptoms of respiratory depression and sedation. Patients and their caregivers should be made aware of these symptoms. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while taking TRAMEDO SR.

Use of opioids in chronic (long-term) non-cancer pain (CNCP)

Opioid analgesics have an established role in the treatment of acute pain, cancer pain and palliative and end-of-life care. Current evidence does not generally support opioid analgesics in improving pain and function for most patients with chronic non-cancer pain. The development of tolerance and physical dependence and risks of adverse effects, including hazardous and harmful use, increase with the length of time a patient takes an opioid. The use of opioids for long-term treatment of CNCP is not recommended.

The use of an opioid to treat CNCP should only be considered after maximised nonpharmacological and non-opioid treatments have been tried and found ineffective, not tolerated or otherwise inadequate to provide sufficient management of pain. Opioids should only be prescribed as a component of comprehensive multidisciplinary and multimodal pain management.

Opioid therapy for CNCP should be initiated as a trial in accordance with clinical guidelines and after a comprehensive biopsychosocial assessment has established a cause for the pain and the appropriateness of opioid therapy for the patient (see Hazardous and harmful use, above). The expected outcome of therapy (pain reduction rather than complete abolition of pain, improved function and quality of life) should be discussed with the patient before commencing opioid treatment, with agreement to discontinue treatment if these objectives are not met.

Owing to the varied response to opioids between individuals, it is recommended that all patients be started at the lowest appropriate dose and titrated to achieve an adequate level of analgesia and functional improvement with minimum adverse reactions. Immediate-release products should not be used to treat chronic pain, but may be used for a short period in opioidnaïve patients to develop a level of tolerance before switching to a modified-release formulation. Careful and regular assessment and monitoring is required to establish the clinical need for ongoing treatment. Discontinue opioid therapy if there is no improvement of pain and/or function during the trial period or if there is any evidence of misuse or abuse.

Treatment should only continue if the trial has demonstrated that the pain is opioid responsive and there has been functional improvement. The patient's condition should be reviewed regularly and the dose tapered off slowly if opioid treatment is no longer appropriate (see Ceasing Opioids).

Tolerance, dependence and withdrawal

Neuroadaptation of the opioid receptors to repeated administration of opioids can produce tolerance and physical dependence. Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid.

Physical dependence, which can occur after several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dose is significantly reduced. Withdrawal symptoms can also occur following the administration of an opioid antagonist (e.g. naloxone) or partial agonist (e.g. buprenorphine). Withdrawal can result in some or all of the following symptoms: dysphoria, restlessness/agitation, lacrimation, rhinorrhoea, yawning, sweating, chills, myalgia, mydriasis, irritability, anxiety, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate and increased heart rate.

Symptoms of withdrawal reactions from tramadol hydrochloride are similar to those occurring during opiate withdrawal and may include: 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).

When discontinuing TRAMEDO SR in a person who may be physically-dependent, the drug should not be ceased abruptly but withdrawn by tapering the dose gradually (see Ceasing opioids and section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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.

Accidental ingestion/exposure

Accidental ingestion or exposure of TRAMEDO SR, especially by children, can result in a fatal overdose of tramadol hydrochloride. Patients and their caregivers should be given information on safe storage and disposal of unused TRAMEDO SR (see section 6.4 SPECIAL PRECAUTIONS FOR STORAGE and section 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL).

Hyperalgesia

Hyperalgesia may occur with the use of opioids, particularly at high doses. Hyperalgesia may manifest as an unexplained increase in pain, increased levels of pain with increasing opioid dosages or diffuse sensitivity not associated with the original pain. Hyperalgesia should not be confused with tolerance (see Tolerance, dependence and withdrawal). If opioid induced hyperalgesia is suspected, the dose should be reduced and tapered off if possible. A change to a different opioid may be required.

Ceasing opioids

Abrupt discontinuation or rapid decreasing of the dose in a person physically dependent on an opioid may result in serious withdrawal symptoms and uncontrolled pain (see Tolerance, dependence and withdrawal). Such symptoms may lead the patient to seek other sources of licit or illicit opioids. Opioids should not be ceased abruptly in a patient who is physically dependent but withdrawn by tapering the dose slowly. Factors to take into account when deciding how to discontinue or decrease therapy include the dose and duration of the opioid the patient has been taking, the type of pain being treated and the physical and psychological attributes of the patient. A multimodal approach to pain management should be in place before initiating an opioid analgesic taper. During tapering, patients require regular review and support to manage any increase in pain, psychological distress and withdrawal symptoms.

There are no standard tapering schedules suitable for all patients and an individualised plan is necessary. In general, tapering should involve a dose reduction of no more than 10 percent to 25 percent every 2 to 4 weeks (see section 4.2 DOSE AND METHOD OF ADMINISTRATION). If the patient is experiencing increased pain or serious withdrawal symptoms, it may be necessary to go back to the previous dose until stable before proceeding with a more gradual taper.

When ceasing opioids in a patient who has a suspected opioid use disorder, the need for medication assisted treatment and/or referral to a specialist should be considered.

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, has been reported in patients receiving tramadol in combination with other serotonergic agents or tramadol alone (see sections 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and 4.9 OVERDOSE).

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose escalations.

Symptoms of serotonin syndrome may include mental status changes (including anxiety, agitation, and confusion), autonomic instability (including diaphoresis, tachycardia, hyperthermia, hypertension, vomiting, and diarrhoea), and neuromuscular abnormalities (including muscle rigidity, myoclonus, tremor, and hyperreflexia).

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms. Withdrawal of the serotonergic drugs usually brings about a rapid improvement.

Acute abdominal conditions

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

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.

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

CYP2D6 metabolism

Tramadol is metabolised by the liver enzyme CYP2D6. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect may not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an ultra-rapid metaboliser there is a risk of developing side effects of opioid toxicity even at commonly prescribed doses.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, miosis, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised below:

Table 1: Prevalence of ultra-rapid metabolisers in different populations

Population	Prevalence %
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1% to 2%

Adrenal insufficiency

Opioid analgesics may occasionally cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of acute or chronic adrenal insufficiency may include e.g. severe abdominal pain, nausea and vomiting, low blood pressure, extreme fatigue, decreased appetite, and weight loss.

Endocrine effects

Opioids, such as tramadol, may influence the hypothalamic-pituitary-adrenal or –gonadal axes. Hormonal disturbances that have been observed include an increase in serum prolactin and decreases in plasma cortisol and testosterone. Clinical symptoms may manifest from these hormonal changes.

Androgen deficiency may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility.

Neonatal Withdrawal Syndrome

Chronic use of tramadol by the mother at the end of pregnancy may result in a withdrawal syndrome (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, convulsions, apnoea or bradycardia) in the neonate. In many reported cases the withdrawal was serious and required treatment. The syndrome is generally delayed for several hours to several days after birth. (See section 4.6 – USE IN PREGNANCY).

Hepatobiliary disorders

Opioids may cause dysfunction and spasm of the sphincter of Oddi, thus raising intrabiliary pressure and increasing the risk of biliary tract symptoms and pancreatitis. Therefore, tramadol has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

Gastrointestinal Toxicity

Reports of significant oesophageal dysfunction have been observed via high-resolution manometry in patients taking opioid medicines on a long-term basis. Discontinuation or weaning of opioids should be considered in patients presenting with oesophageal complaints including but not limited to dysphagia, regurgitation, or non-cardiac chest pain.

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 below – Use in hepatic impairment & Use in renal impairment).

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 or prolongation of the dosage intervals should be carefully considered according to the patient's requirements (see section 4.2 DOSE AND METHOD OF ADMINISTRATION and section 5.2 - PHARMACOKINETIC PROPERTIES).

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 only removed very slowly by haemodialysis or haemofiltration, postdialysis administration to maintain analgesia is not usually necessary (see section 4.2 - DOSE AND METHOD OF ADMINISTRATION and section 5.2 PHARMACOKINETIC PROPERTIES).

Use in the elderly

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 (see section 5.2 -PHARMACOKINETIC PROPERTIES).

Paediatric use

The use of tramadol hydrochloride is contraindicated in all children younger than 12 years of age and in postoperative management of children younger than 18 years of age following tonsillectomy and/or adenoidectomy.

Post-operative use in children

There have been reports in the published literature that tramadol given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life threatening adverse events.

Extreme caution should be exercised when tramadol is administered to children for post-operative pain relief and should be accompanied by close monitoring for symptoms of opioid toxicity including respiratory depression.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Use with 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, benzodiazepines, gabapentinoids, cannabis, tricyclic antidepressants, antipsychotics, antihistamines and centrally-active anti-emetics (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Risks from concomitant use of benzodiazepines or other CNS depressants including alcohol).

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 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), tricyclics antidepressants and mirtazapine may cause serotonin syndrome (see sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.8 ADVERSE

EFFECTS (UNDESIRABLE EFFECTS)).

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) 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 section 4.3 CONTRAINDICATIONS).

Anticholinergics

Concomitant administration of opioids with anticholinergics or medications with anticholinergic activity may result in increased anticholinergic adverse effects.

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 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 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 post-operative 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 – 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 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 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. Tramadol crosses the placenta.

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 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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Due to its sedative effect, patients should be advised to avoid driving or operating heavy machinery while taking tramadol. Even when taken according to instructions, tramadol may cause effects such as somnolence and dizziness and therefore may impair the reactions of drivers and machine operators. This applies particularly in conjunction with other psychotropic substances, particularly alcohol.

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 (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

Not known: Adrenal insufficiency

Androgen deficiency

Cases of SIADH (syndrome of inappropriate antidiuretic hormone secretion) have been reported in literature.

Metabolism and nutrition disorders

Rare: Changes in appetite

Not known: Hypoglycaemia

Cases of hyponatremia have been reported in literature.

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), physical dependence, withdrawal syndrome (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Tolerance, dependence and withdrawal and ceasing opioids).

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

Not known: Serotonin syndrome

Eye disorders

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

Cardiac disorders

Uncommon: Tachycardia, flushing, palpitations.

Rare: Bradycardia

Vascular disorders

Uncommon: Orthostatic dysregulation (postural hypotension, 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)

Not Known: Hiccups, central sleep apnoea syndrome

Gastrointestinal disorders

Very common: Nausea

Common: Vomiting, constipation, dry mouth.

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

Not known: Pancreatitis

Hepatobiliary disorders

Very rare: Elevated liver enzymes

Not known: Spasm of sphincter of Oddi

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.

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 www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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, respiratory arrest and death.

Serotonin syndrome has also been reported.

Toxic leukoencephalopathy has been observed with opioid overdose.

Treatment

Should overdosage occur, general emergency measures should be implemented. Keep the respiratory airways open and maintain respiration and circulation.

If over dosage is due to ingestion of an oral dose form, 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 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 haemo filtration. 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 Poisons Information Centre on 13 11 26 (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 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.

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 development has been reported to be relatively mild.

Clinical trials

No data available

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

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%).

The administration of tramadol (sustained release) every 12 hours and tramadol (immediate release) every six hours at the same total daily dose resulted in similar peak and trough serum tramadol concentrations and total tramadol exposure for the two preparations.

Table 2: 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 section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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 renal impairment including subjects with a considerably decreased CLCr [< 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 Cmax and total exposure are increased by 30 and 50%, respectively, but the half-life of tramadol is only slightly prolonged (by 15%) (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 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.

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 PARTICULARS

6.1 LIST OF EXCIPIENTS

The excipients contained in each of the three strengths of TRAMEDO SR include calcium hydrogen phosphate dihydrate, hyprolose, colloidal anhydrous silica and magnesium stearate.

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^{o}C

6.5 NATURE AND CONTENTS OF CONTAINER

TRAMEDO SR tablets in blisters in a carton:

- 100 mg tramadol hydrochloride: 20's;
- 150 mg tramadol hydrochloride: 20's;
- 200 mg tramadol hydrochloride: 20's.

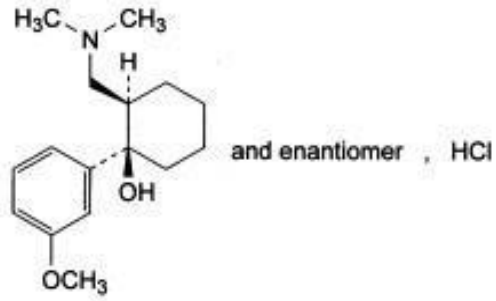
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking 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. The water/n-octanol partition coefficient is 1.35 at pH 7.

Chemical structure



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

Molecular Formula: $C_{16}H_{25}NO_2.HCl$

Molecular Weight: 299.84

CAS number

53611-16-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 Prescription Medicine

8 SPONSOR

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Box Hill, VIC, 3128

Distributor

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Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

6 March 2009

10 DATE OF REVISION

02 December 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Added opioid class warnings for endocrine effects, neonatal withdrawal syndrome, hepatobiliary disorders, and gastrointestinal toxicity.
4.8	Added adverse reactions with frequency not known: Pancreatitis, spasm of sphincter of Oddi, adrenal insufficiency and androgen deficiency .
4.9	Added statement 'toxic leukoencephalopathy has been observed with opioid overdose.

TRAMEDO® is a Viatris company trade mark