PROFESSIONAL INFORMATION

SCHEDULING STATUS

Schedule 5

1. NAME OF THE MEDICINE

TRAMAL® SR 50 mg tablet

TRAMAL® SR 100 mg tablet

TRAMAL® SR 150 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TRAMAL SR 50 mg contains 50 mg tramadol hydrochloride

TRAMAL SR 100 mg contains 100 mg tramadol hydrochloride.

TRAMAL SR 150 mg contains 150 mg tramadol hydrochloride.

Contains sugar (lactose monohydrate)

Each tablet contains 2,5 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

TRAMAL SR 50 mg:	Pale yellow, round, biconvex, film-coated tablet. Engraved T0/Grünenthal logo.
TRAMAL SR 100 mg:	White, round, biconvex, film-coated tablet. Engraved T1/Grünenthal logo.
TRAMAL SR 150 mg:	Pale-orange, round, biconvex, film-coated tablet. Engraved T2/Grünenthal logo.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Management of moderate to severe pain.

4.2 Posology and method of administration

Posology

The dosage should be adjusted to the intensity of pain and the sensitivity of the individual patient.

Adults and children over 12 years:

The usual initial dose is 100 mg twice daily, to be taken whole, not divided or chewed, with sufficient liquid, with or without meals, preferably mornings and evenings. If pain relief is not adequate, the dose may be increased to 150 mg or 200 mg twice daily.

A total daily dose of 400 mg TRAMAL SR should not be exceeded.

Dosage intervals can be adjusted to individual requirements but should be at least 8 hours. The lowest analgesically effective dose should generally be selected.

Children

On account of the dosage strength, TRAMAL SR is not recommended for children below the age of 12 years.

Elderly

A downward adjustment of the dose and/or prolongation of the interval between doses are recommended in the elderly (over 75 years).

Renal Insufficiency/Dialysis

In patients with renal insufficiency the elimination of tramadol hydrochloride 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 SR tablets are not recommended.

Patients with hepatic impairment

In patients with hepatic insufficiency the elimination of tramadol hydrochloride is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements. In cases of severe hepatic insufficiency TRAMAL SR tablets are not recommended.

Duration of treatment

Under no circumstances should TRAMAL SR be given for longer than absolutely necessary. If the nature and severity of the disease requires long-term pain treatment, careful checks should be carried out initially and at regular intervals to assess efficacy and adverse events, and to what extent further treatment with TRAMAL SR is necessary.

4.3 Contraindications:

- All Children younger than 12 years of age (See section 4.4)
- Postoperative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy.
- Known hypersensitivity to tramadol hydrochloride or opioids or any of the ingredients of TRAMAL SR.
- in acute intoxication with alcohol, hypnotics, analgesics, opioids or psychotropic medicines.
- It should not be administered to patients who are receiving monoamine oxidase (MAO) inhibitors or within two weeks of their withdrawal.
- TRAMAL SR should not be given to patients with epilepsy.

TRAMAL SR must not be used for narcotic withdrawal treatment.

TRAMAL SR should not be given to patients with respiratory depression, or in the presence of cyanosis and excessive bronchial secretions.

TRAMAL SR should not be given to patients with increased intracranial pressure or central nervous depression due to head injury or cerebral disease.

TRAMAL SR should not be used in pregnant and breastfeeding women (see PREGNANCY AND LACTATION).

4.4 Special warnings and precautions for use

TRAMAL SR is not suitable for children under the age of 12 years.

TRAMAL SR should be used with care in patients with increased reactivity to opioids.

Respiratory depression may develop if the recommended dosages are exceeded or other centrally depressant medicines are given concomitantly.

Tramal SR should not be used in the treatment of minor pain.

TRAMAL SR should be used with caution in patients with impairment of hepatic and renal function and in patients prone to convulsive disorders or in shock (See DOSAGE AND DIRECTIONS FOR USE).

Seizures

Seizures have been reported in patients receiving TRAMAL SR at dosages within the recommended dosage range. The risk of seizures may be enhanced in patients exceeding the recommended dose, or in patients taking tricyclic anti-depressants or other tricyclic compounds e.g. promethazine, selective serotonin re-uptake inhibitors, MAO-inhibitors and neuroleptics. The risk of seizures may also be increased in patients with epilepsy; with a history of seizures or in patients with a recognised risk for seizures e.g. drug and alcohol withdrawal, intracranial

infections, head trauma, metabolic disorders and naloxone administration with Tramal overdose.

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia.

Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Drug Abuse and Dependence

Tolerance, psychic and physical dependence of the morphine-type (μ opioid) may develop.

TRAMAL SR has been associated with craving drug-seeking behaviour and tolerance development. After discontinuation of TRAMAL SR signs of withdrawal may appear. Symptoms of withdrawal syndrome similar to those occurring during opiate withdrawal, may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesias, tremor and gastro-intestinal symptoms.

Other symptoms that have been seen with TRAMAL SR discontinuation include: panic attacks; severe anxiety, hallucinations, paraesthesias, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalisation, derealisation, paranoia).

TRAMAL SR should not be used in opioid-dependent patients. TRAMAL SR can reinstate physical dependence in patients that have been previously dependent or chronically using other

opioids. In patients with a tendency to drug abuse, a history of drug dependence or who are chronically using opioids, treatment with TRAMAL SR is not recommended.

Opioid induced hyperalgesia

Opioid induced hyperalgesia (OIH) is a paradoxical response to an opioid in which there is an increase in pain perception despite stable or increased opioid exposure. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain. OIH may manifest as increased levels of pain, more generalized pain (i.e., less focal), or pain from ordinary (i.e. non-painful) stimuli (allodynia) with no evidence of disease progression. When OIH is suspected, the dose of opioid should be reduced or tapered off, if possible.

CYP2D6 Ultra-rapid metabolism of tramadol:

Patients who are CYP2D6 ultra-rapid metabolisers may convert tramadol to its active metabolite (M1) more rapidly and completely than other patients. This rapid conversion may lead to higher than expected serum M1 levels which could lead to an increased risk of respiratory depression. Alternative medication, dose reduction and/or increased monitoring for signs of tramadol overdose, such as respiratory depression is recommended in patients known to be CYP2D6 ultra-rapid metabolisers.

Hyponatraemia:

Hyponatraemia has been reported with the use of TRAMAL, usually in patients with

predisposing risk factors, such as elderly patients and/or patients using concomitant medications that may cause hyponatraemia. This hyponatraemia appeared to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and resolved with discontinuation of TRAMAL and appropriate treatment (e.g. fluid restriction). During TRAMAL treatment, monitoring for signs and symptoms of hyponatraemia is recommended for patients with predisposing risk factors.

Lactose

TRAMAL SR contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take TRAMAL SR.

4.5 Interaction with other medicines and other forms of interaction:

TRAMAL SR should not be combined with MAO inhibitors within 14 days of withdrawal of MAO inhibitors (see CONTRAINDICATIONS).

In patients treated with MAO inhibitors in the 14 days prior to the use of the opioid pethidine, life-threatening interactions of the central nervous system, respiratory and cardiovascular function have been observed. The same interactions with MAO inhibitors cannot be ruled out during treatment with TRAMAL SR.

Concomitant administration of TRAMAL SR with other centrally depressant medicines including alcohol may potentiate the CNS effects (see CONTRAINDICATIONS).

Simultaneous or previous administration of carbamazepine (enzyme inducer) may reduce the analgesic effect and shorten the duration of action.

TRAMAL SR can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, anti-psychotics and other seizure threshold-lowering medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.

Concomitant therapeutic use of TRAMAL SR and serotoninergic medicinal products such as selective serotonin re-uptake inhibitors (SSRIs), MAO inhibitors, tricyclic antidepressants and mirtazapine may cause serotonin toxicity. The serotonin syndrome is likely when one of the following is observed:

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

Withdrawal of the serotoninergic medicinal products usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

Caution should be exercised during concomitant treatment with TRAMAL SR and warfarin–like medicines due to reports of increased International Normalised Ratio (INR) with major bleeding and ecchymoses in some patients.

The inhibition of one or both types of isoenzymes CYP3A4 and CYP2D6 involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolite.

Other active substances known to inhibit CYP3A4, such as ketoconazole and erythromycin, might inhibit the metabolism of tramadol (N-demethylation) probably also the metabolism of the active O-demethylated metabolite. The clinical importance of such an interaction has not been studied (see Pharmacokinetic properties).

The antiemetic 5-HT3 antagonist ondansetron increased the requirement of TRAMAL SR in patients with postoperative pain. TRAMAL SR may decrease the antiemetic efficacy of ondansetron.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety during pregnancy and lactation has not been established.

Therefore TRAMAL SR tablets should not be used in pregnant women. TRAMAL SR crosses the placenta. Animal studies with TRAMAL SR revealed effects on organ development, ossification and neonatal mortality.

The repeated administration of TRAMAL SR tablets during pregnancy may lead to habituation in the unborn child. The child may experience withdrawal symptoms after birth (see CONTRAINDICATIONS).

Breastfeeding

TRAMAL SR passes into breastmilk. Mothers on TRAMAL SR tablets should not breastfeed their infants.

4.7 Effects on ability to drive or operate machinery

TRAMAL SR may affect reactions to the extent that driving ability and the ability to operate machinery may be impaired.

4.8 Undesirable effects

SIDE EFFECTS

TRAMAL SR tablets may have side effects. These are classified as follows:

- very common (≥1/10)
- common (≥1/100, <1/10)
- uncommon (≥1/1000, <1/100)
- rare (≥1/10 000, <1/1000)
- very rare (<1/10 000, including isolated reports)

Clinical Trial Data

The common side effects during treatment with TRAMAL SR tablets are nausea and dizziness

Immune system disorders

Rare:	allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioedema) and anaphylaxis.

Metabolism and nutrition disorders

Rare:	changes in appetite

Psychiatric disorders

Rare:	hallucinations, confusional states, sleep disorders, delirium, anxiety and nightmares. Changes in mood (euphoria, dysphoria), decreased activity, restlessness and changes in cognitive and sensory perception (such as decision behaviour, perception disorders).

Nervous system disorders

Very common:	dizziness
Common:	headaches, somnolence
Rare:	speech disorders, paraesthesia, tremor, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope

Eye disorders

Rare:	miosis, mydriasis, blurred vision

Cardiac disorders

Uncommon:	dysrhythmias, palpitation, tachycardia.
Rare:	bradycardia

Vascular disorders:

Uncommon:	postural hypotension, cardiovascular collapse
Rare:	increase in blood pressure

Respiratory, thoracic and mediastinal disorders

Rare:	respiratory depression, dyspnoea, bronchospasm

Gastrointestinal disorders

Very common:	nausea
Common:	vomiting, constipation, dry mouth.
Uncommon:	retching, gastrointestinal discomfort.

Hepatobiliary disorders

Very rare:	increase in transaminases (ALT and AST) is expected

Skin and subcutaneous tissue disorders

Common:	hyperhidrosis
Uncommon:	dermal reactions (e.g. itching, rash, urticaria).

Musculoskeletal, connective tissue and bone disorders

Rare: muscular weakness

Renal and urinary disorders

Rare: micturition disorders (dysuria and urinary retention)

General disorders and administration site conditions

Common: fatigue

Post-marketing experience

The following post-marketing experiences have been reported:

Nervous system disorders

Speech disorders

Eye disorders

Mydriasis

Skin and subcutaneous tissue disorders

Stevens Johnson Syndrome

Toxic Epidermal Necrolysis

Cases of hyponatraemia and/or SIADH have been reported in patients taking tramadol, usually in patients with predisposing risk factors, such as the elderly or those using concomitant medications that may cause hyponatraemia.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine product is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via "6.04 Adverse Drug Reaction Reporting Form" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/index/8

Alternatively, suspected adverse reactions may be reported directly to Janssen Pharmaceutica (see section 7 for contact details or visit www.janssen.com).

4.9 Overdose Symptoms

Following an overdose with TRAMAL SR, symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include in particular constriction of the pupil of the eye, vomiting, cardiovascular collapse, consciousness disorders, coma, convulsions, respiratory depression and respiratory arrest.

Treatment

The general emergency measures apply. Keep open the airway, prevent aspiration and, maintain respiration and circulation depending on the symptoms. Suitable measures should be taken to avoid aspiration dangers.

Respiratory depression can be antagonised with a pure opiate antagonist (naloxone). Convulsions should be treated with intravenous diazepam.

In cases of overdosage with oral formulations, gastrointestinal-decontamination with activated charcoal is only recommended within 2 hours after TRAMAL SR intake. Gastrointestinal decontamination at a later time point may be useful in case of overdosage with exceptionally large quantities.

Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Treatment of acute intoxication with TRAMAL SR with haemodialysis or haemofiltration alone is therefore not suitable for detoxification.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification

A.2.9. Other analgesics

Mechanism of action

Tramadol hydrochloride is a centrally acting analgesic with binding to specific opioid receptors. It is a non-selective agonist at mu (μ), delta (δ), and kappa (k) opioid receptors with higher affinity for the μ receptor. Other mechanisms, which contribute to its analgesic effect, are inhibition of neuronal re-uptake of noradrenaline as well as the enhancement of serotonin release. Tramadol hydrochloride crosses the blood-brain and placental barrier. Small amounts are excreted in breast milk unchanged or as the metabolite M1.

The relationship between serum concentrations and the analgesic effect is dose-dependent, but varies considerably.

Patients devoid of CYP2D6 may need higher doses of tramadol, to achieve adequate analgesia.

5.2 Pharmacokinetic properties

Under steady-state conditions the following was observed for tramadol in a sustained release preparation:

After oral administration of TRAMAL SR, tramadol is absorbed.

The absolute bioavailability is approximately 70 % following a single dose and increases to approximately 90 % at steady state. Cmax (141 ± 40 ng/mℓ) is reached 4.9 hours after oral administration of TRAMAL SR 100 mg and 4.8 hours (Cmax 260 ± 62 ng/mℓ) after oral administration of TRAMAL SR 200 mg.

Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range. The elimination half-life is 5 to 7 hours. Tramadol is mainly metabolised in the liver (90 %).

Tramadol hydrochloride and its metabolites are almost completely excreted by the renal route (95 %). Biliary excretion of these components is quantitatively insignificant and is therefore subject to hepatic metabolism and renal elimination. The terminal half-life ($t_{½\beta}$) is prolonged in impaired hepatic or renal function. In patients with liver cirrhosis, the mean $t_{½\beta}$ of tramadol was 13,3 ± 4,9 h, $t_{½,\beta}$/M1 18,5 ± 9,4 h, in patients with renal insufficiency (creatinine clearance ≤ 5 mℓ/min) the values were 11,0 ± 3,2 h (tramadol) and 16,9 ± 3,0 h (M1) respectively.

The inhibition of one or both types of isoenzymes CYP3A4 and CYP2D6 involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolite.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Inactive ingredients: Microcrystalline cellulose, hypromellose, magnesium stearate, colloidal anhydrous silica, lactose monohydrate, macrogol 6000, propylene glycol, talc, titanium dioxide, TRAMAL SR 50/150/~~200~~ mg tablets also contain quinoline yellow and iron oxides. (Contains lactose :See section 4.4)

6.2 Incompatibilities:

Not Applicable.

6.3 Shelf life:

60 Months

6.4 Special precautions for storage:

Store in a cool, dry place, at or below 25 ^{0}C.

KEEP OUT OF REACH OF CHILDREN

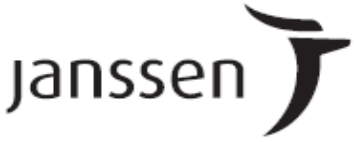
6.5 Nature and contents of container:

Folding carton box containing 10, 30, 60 or 100 tablets in blister strips of 10's. The blister strips are white & opaque PVC/PVDC - aluminium blister foil packs or white & opaque PP- Aluminium blister foil packs.

6.6 Special precautions for disposal and other handling:

No Special Requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION



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8. REGISTRATION NUMBER

TRAMAL SR 50 mg: 42/2.9/0283

TRAMAL SR 100 and 150: 31/2.9/0646/7

9. DATE OF FIRST AUTHORISATION

- Date on the registration certificate:
    - TRAMAL SR 50 mg: 7 December 2012
    - TRAMAL SR 100 and 150 mg: 03 September 2001

10. DATE OF REVISION OF THE TEXT

- Date of the last approved professional information: 15 July 2021