SUMMARY OF PRODUCT CHARACTERISTICS

TRAMA-50 Injection (Tramadol Hydrochloride 50 mg/mL Solution for Injection)

1. NAME OF THE MEDICINAL PRODUCT

TRAMA-50 Injection (Tramadol Hydrochloride 50 mg/mL Solution for Injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains tramadol hydrochloride 50 mg.

Each 2 mL ampoule contains tramadol hydrochloride 100 mg.

Excipients with known effect:

None

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

A clear, colourless solution, free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TRAMA-50 Injection is indicated for the treatment of moderate to severe pain.

4.2 Posology and method of administration

The dose should be adjusted to the intensity of pain and the individual patient's requirements. The lowest effective dose for analgesia should generally be selected. The total daily dose of 400 mg tramadol should not be exceeded, except in special clinical circumstances (e.g. cancer pain, severe post-operative pain).

Adults and adolescents ≥12 years

50–100 mg (1–2 mL) every 4–6 hours. Maximum total daily dose 400 mg.

Elderly patients

No dose adjustment usually required up to 75 years of age in the absence of significant hepatic or renal insufficiency. In patients >75 years, elimination may be prolonged — extend dosing intervals as required.

Renal and hepatic insufficiency

Elimination of tramadol is delayed; carefully consider extending dosing intervals according to individual requirements.

Paediatric population

Not recommended for children under 1 year of age. For children up to 12 years: single dose 1–2 mg/kg body weight; maximum daily dose 8 mg/kg or 400 mg (whichever is lower).

Duration of administration

Tramadol should not be administered for longer than absolutely necessary. If long-term treatment is necessary, careful and regular monitoring should be performed, including breaks in treatment, to assess ongoing need.

Method of administration

Intravenous (slow injection at 1 mL/50 mg per minute), intramuscular or subcutaneous injection. May also be diluted in 0.9% sodium chloride or 5% glucose solution for infusion.

4.3 Contraindications

- Hypersensitivity to tramadol hydrochloride or to any of the excipients listed in section 6.1.
- Acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic medicinal products.
- Concomitant treatment with monoamine oxidase inhibitors (MAOIs) or within 14 days of their withdrawal.
- Uncontrolled epilepsy.

- Use in patients receiving opioid withdrawal treatment.

4.4 Special warnings and precautions for use

Seizure risk

Tramadol lowers the seizure threshold. Use with caution in patients with epilepsy or those susceptible to seizures. Seizures have occurred at high doses and with concomitant use of serotonergic drugs, tricyclic antidepressants, antipsychotics and other agents that lower the seizure threshold.

Serotonin syndrome

Concomitant use with serotonergic drugs (SSRIs, SNRIs, MAOIs, tricyclic antidepressants, mirtazapine) may cause serotonin syndrome, characterised by spontaneous clonus, inducible clonus with agitation, tremor, hyperreflexia, hypertonia and fever >38°C. Withdraw serotonergic drugs promptly if serotonin syndrome develops.

CYP2D6 pharmacogenetics

Tramadol is metabolised by CYP2D6 to its active O-desmethyl metabolite. Patients who are CYP2D6 poor metabolisers may have inadequate analgesia. Ultra-rapid metabolisers are at risk of opioid toxicity (confusion, somnolence, shallow breathing, small pupils, nausea, vomiting) even at standard doses.

Dependence and withdrawal

Tramadol has opioid-like properties and may cause dependence. Withdrawal symptoms (agitation, anxiety, insomnia, tremor, GI symptoms) may occur. In rare cases, discontinuation may precipitate panic attacks, hallucinations and abnormal CNS symptoms.

Post-operative use in children

Life-threatening events have been reported in children who received tramadol post-operatively after tonsillectomy/adenoidectomy for obstructive sleep apnoea. Extreme caution is advised; tramadol is not recommended in children with compromised respiratory function.

Respiratory depression

Respiratory depression may occur with significant overdose or concomitant CNS depressants. Caution in patients with respiratory depression, head injury, increased intracranial pressure or reduced level of consciousness.

4.5 Interaction with other medicinal products and other forms of interaction

MAOIs (contraindicated):

Life-threatening interactions affecting CNS, respiratory and cardiovascular function.

Serotonergic drugs (SSRIs, SNRIs, MAOIs, TCAs, mirtazapine):

Risk of serotonin syndrome.

CNS depressants (including alcohol):

Potentiation of CNS effects including respiratory depression.

Coumarin derivatives (e.g. warfarin):

Increased INR with major bleeding and ecchymoses reported; monitor INR.

Carbamazepine (CYP3A4 inducer):

May reduce analgesic effect and shorten duration of action.

CYP3A4 inhibitors (ketoconazole, erythromycin):

May inhibit metabolism of tramadol and active metabolite.

Cimetidine:

Pharmacokinetic interaction unlikely to be clinically relevant.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies at very high doses show effects on organ development, ossification and neonatal mortality. Tramadol crosses the placenta. Insufficient evidence for safety in human pregnancy; should not be used. Tramadol given before or during birth does not affect uterine contractility but may affect neonatal respiratory rate. Prolonged use in pregnancy may lead to neonatal withdrawal symptoms.

Breast-feeding

Approximately 0.1% of maternal tramadol dose is excreted in breast milk. Should not be used during lactation, or breast-feeding should be discontinued. Discontinuation of breast-feeding is generally not necessary following a single therapeutic dose.

Fertility
No specific data.

4.7 Effects on ability to drive and use machines
TRAMA-50 Injection may cause somnolence and dizziness and impair reactions. Patients should not drive or operate machinery. This applies particularly in conjunction with alcohol or other psychotropic substances.

4.8 Undesirable effects
Very common (≥1/10): Dizziness, nausea. Common: Headache, somnolence, constipation, dry mouth, vomiting, hyperhidrosis, fatigue. Uncommon: Palpitations, tachycardia, postural hypotension or cardiovascular collapse (especially on IV administration or in physically stressed patients), diarrhoea, dermal reactions (pruritus, rash, urticaria). Rare: Bradycardia, increased blood pressure, paraesthesia, tremor, epileptiform convulsions, involuntary muscle contractions, syncope, speech disorders, hallucinations, confusion, sleep disturbance, delirium, miosis, mydriasis, blurred vision, respiratory depression, dyspnoea, micturition disorders. Very rare: Elevated liver enzymes. Drug dependence may occur.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the National Regulatory Authority.

4.9 Overdose
Symptoms
Similar to opioid intoxication: miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions, respiratory depression up to respiratory arrest.

Treatment
General emergency measures — maintain open airway, respiration and circulation. Naloxone is the antidote for respiratory depression (note: in animal experiments naloxone had no effect on convulsions). Diazepam IV should be used for convulsions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Analgesics, other opioids. ATC code: N02AX02.

Tramadol is a centrally acting opioid analgesic. It is a non-selective pure agonist at μ, δ and κ opioid receptors with higher affinity for the μ receptor. Additional mechanisms contributing to analgesia include inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release. The potency of tramadol is approximately 1/10 to 1/6 that of morphine. Analgesic doses over a wide range do not cause respiratory depression, and gastrointestinal motility is less affected than with conventional opioids.

5.2 Pharmacokinetic properties
After parenteral administration, tramadol is rapidly and almost completely absorbed; bioavailability approximately 100% following IM injection. High tissue affinity; apparent volume of distribution approximately 2.6–2.9 L/kg. Plasma protein binding approximately 20%. Extensively hepatically metabolised (primarily CYP2D6 and CYP3A4) to O-desmethyltramadol (active) and N-desmethyltramadol (inactive). Tramadol and its metabolites are eliminated mainly by the kidneys (approximately 90% in urine). Elimination half-life approximately 6 hours.

5.3 Preclinical safety data
Repeated oral and parenteral administration at doses well above the therapeutic range caused CNS manifestations in rats and dogs. Reproductive toxicity observed in rats and rabbits at high, maternally toxic doses (ossification disorders, reduced pregnancy rate). Tramadol can be classified as non-mutagenic based on available in vivo data (some in vitro evidence of mutagenicity). Long-term carcinogenicity studies showed no substance-related increase in tumours in rats; an increase in liver adenomas and pulmonary tumours in mice at high doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium acetate anhydrous, disodium edetate, water for injections.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store in a cool place below 30°C. Protect from light. Do not freeze. Keep out of the reach and sight of children.

6.5 Nature and contents of container
2 mL clear glass ampoules. Cartons containing 10 ampoules (2 × 5 ampoules per pack).

6.6 Special precautions for disposal and other handling
No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
CACHET PHARMACEUTICALS PRIVATE LIMITED

415, Shah Nahar Industrial Estate,

Dr. E. Moses Road, Worli, Mumbai 400018,

Maharashtra, India.

8. MARKETING AUTHORISATION NUMBER (PPB REGISTRATION NUMBER)
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