

SUMMARY OF PRODUCT CHARACTERISTICS

1.Name of the Medicinal Product: Brand Name:

TRAMA-50 Tramadol Injection BP 50mg

2. Qualitative and Quantitative Composition

Each ml contains:

Tramadol Hydrochloride BP ...50 mg

For the full list of excipients, See Section 6.1

3. Pharmaceutical Form:

Liquid for Injection (IM/IV Use)

4. Clinical Particulars

4.1Therapeutic Indications

Treatment of moderate to severe pain.

4.2. Posology and Method of Administration:

The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient. 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 (for example, in case of cancer pain or postoperative severe pain).

Unless otherwise prescribed, Tramadol should be administered as follows:

Adults and adolescents above the age of 12 years

Depending on the intensity of pain, 50- 100 mg of tramadol (corresponds to 1-2 ml of Tramadol) is administered every 4- 6 hours. The total daily dose of 400 mg should not be exceeded.

Elderly patients

A dose adjustment is not usually necessary in patients up to 75 years without clinically manifest hepatic or renal insufficiency. In patients over 75 years elimination may be prolonged. Therefore, if necessary, the dosage interval is to be extended according to individual requirements.

Renal insufficiency/dialysis and hepatic insufficiency

In patients with renal and/or hepatic insufficiency the elimination of tramadol is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patients requirements.

Paediatric population

Tramadol should not be used in children under 1 year of age.

For children up to the age of 12, the single dose of tramadol is 1-2 mg per kg body

weight. The lowest effective dose for analgesia should generally be selected. The total daily dose must not exceed the lowest of these doses - 8 mg/kg body weight or 400 mg of the active substance.

Method of administration

Intravenous (solution is to be injected slowly (1 ml (50 mg of tramadol hydrochloride) per minute)), intramuscular or subcutaneous injection. Tramadol may also be diluted in solution for infusion (for example, 0.9% sodium chloride or 5% glucose solution) and infused.

Duration of administration

Tramadol should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with tramadol is necessary in view of the nature and severity of the illness, then careful and regular monitoring should be carried out (if necessary with breaks in treatment) to establish whether and to what extent further treatment is necessary.

4.3 Contraindications:

Hypersensitivity to the active substance and/or to any of the excipients listed.

Acute intoxication with alcohol, hypnotics, analgesics, opioids, or other psychotropic medicinal products.

4.4 Special Warnings and Precautions for Use:

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, small pupils, 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.

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.

Children with compromised respiratory function

Tramadol is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of opioid toxicity.

Tramadol may only be used with particular caution in opioid-dependent patients, patients with head injury, shock, a reduced level of consciousness of uncertain origin, disorders of the respiratory centre or function, increased intracranial pressure.

In patients sensitive to opiates the product should only be used with caution.

Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered, or if the recommended dosage is significantly exceeded as the possibility of respiratory depression cannot be excluded in these situations.

4.5 Interaction with other medicinal products and other forms of interaction:

MAO inhibitors

Tramadol should not be used in combination with MAO inhibitors.

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

Cimetidine

The results of pharmacokinetic studies have so far shown that on the concomitant or previous administration of cimetidine (enzyme inhibitor) clinically relevant interactions are unlikely to occur.

Carbamazepine

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

CNS-active agents

Concomitant administration of Tramadol with other centrally depressant medicinal products including alcohol may potentiate the CNS effects.

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 medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.

Concomitant therapeutic use of tramadol and serotonergic drugs, such as selective serotonin

reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors, 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 drugs usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

Coumarin derivatives

Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (e.g. warfarin) due to reports of increased INR with major bleeding and ecchymoses in some patients.

CYP3A4 inhibitors

Other active substances known to inhibit CYP3M, such as ketoconazole and erythromycin, might inhibit the metabolism of tramadol (N- demethylation) and probably also the metabolism of the active O-demethylated metabolite.

4.6 Pregnancy and lactation:

Pregnancy

Animal studies with tramadol at very high doses have revealed effects on organ development, ossification and neonatal mortality. Tramadol crosses the placenta. There is inadequate evidence available on the safety of tramadol in human pregnancy. Therefore, tramadol should not be used in pregnant women. Tramadol - administered before or during birth - does not affect uterine contractility. In neonates it may induce changes in the respiratory rate which are usually not clinically relevant. Prolonged use during pregnancy may lead to neonatal withdrawal symptoms.

Lactation

Approximately 0.1 % of the maternal dose of tramadol is excreted in breast milk. In the immediate post-partum period, for maternal oral daily dosage up to 400mg, this corresponds to a mean amount of tramadol ingested by breast-fed infants of 3% of the maternal weight-adjusted dosage. For this reason, tramadol should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not

necessary following a single dose of tramadol.

4.7 Effects on ability to drive and use machines:

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 alcohol and other psychotropic substances.

This class of medicine is in the list of drugs included in regulations under Sa of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
 - The medicine has been prescribed to treat a medical or dental problem and
 - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
 - It was not affecting your ability to drive safely.

4.8 Undesirable effects

The side effects mentioned below are listed according to MedDRA system organ classification. The frequencies are ranked according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $<1/10$), uncommon ($\geq 1/1,000$ to $<1/100$), rare ($\geq 1/10,000$ to $<1/1,000$), very rare ($<1/10,000$), not known (cannot be estimated from the available data).

The most commonly reported adverse reactions are nausea and dizziness. These occur in more than 10% of patients.

Immune system disorders

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

Cardiac disorders

Uncommon: effect on cardiovascular regulation (palpitations, tachycardia). These adverse reactions may occur especially on intravenous administration and in patients who are physically stressed.

Rare: bradycardia.

Investigations

Rare: increase in blood pressure.

Vascular disorders

Uncommon: effect on cardiovascular regulation (postural hypotension or cardiovascular collapse). These adverse reactions may occur especially on intravenous administration and in patients who are physically stressed.

Nervous system disorders

Very common: dizziness.

Common: headache, somnolence.

Rare: paraesthesia, tremor, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope, speech disorders.

Convulsions occurred mainly after administration of high doses of tramadol or after concomitant treatment with medicinal products lowering the seizure threshold.

Metabolism and nutrition disorders

Rare: changes in appetite.

Not known: hypoglycaemia.

Psychiatric disorders

Rare: hallucinations, confusion, sleep disturbance, delirium, anxiety and nightmares.

Psychic adverse reactions may occur following administration of tramadol which vary individually in intensity and nature (depending on personality and duration of treatment). These include changes in mood (usually elation, occasionally dysphoria), changes in activity (usually suppression, occasionally increase) and changes in cognitive and sensorial capacity (e.g. decision behaviour, perception disorders).

Drug dependence may occur. Symptoms of drug withdrawal syndrome, similar to those occurring during opiate withdrawal, may occur. These include: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor 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, depersonalisation, derealisation, paranoia).

Eye disorders

Rare: miosis, mydriasis, blurred vision.

Respiratory, thoracic and mediastinal disorders

Rare: respiratory depression, dyspnoea.

If the recommended doses are considerably exceeded and other centrally

depressant substances are administered concomitantly, respiratory depression may occur.

Worsening of asthma has been reported, though a causal relationship has not been established.

Gastrointestinal disorders

Very common: nausea.

Common: constipation, dry mouth, vomiting.

Uncommon: retching, gastrointestinal discomfort (a feeling of pressure in the stomach, bloating), diarrhoea.

Hepatobiliary disorders

Very rare: in a few isolated cases an increase in liver enzyme values has been reported in a temporal connection with the therapeutic use of tramadol.

Skin and subcutaneous tissue disorders

Common: hyperhidrosis.

Uncommon: dermal reactions (e.g. pruritus, rash, urticaria).

Musculoskeletal and connective tissue disorders

Rare: muscular weakness.

Renal and urinary disorders

Rare: micturition disorders (dysuria and urinary retention).

General disorders and administration site conditions

Common: fatigue.

Reporting of suspected adverse reactions

Healthcare professional are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Reporting System (PvERS)

<https://pv.pharmacyboardkenya.org>.

4.9 Overdose

Symptoms

In principle, on intoxication with tramadol symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include in particular miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Treatment

The general emergency measures should be taken. Keep open the respiratory tract (aspiration), maintain respiration and circulation depending on the symptoms. The antidote for respiratory depression is naloxone. In animal experiments naloxone had

no effect on convulsions. In such cases diazepam should be given intravenously.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: analgesics, other opioids, ATC code: N02AX02

Mechanism of action

Tramadol is a centrally acting opioid analgesic. It is a non-selective pure agonist at μ , δ and κ opioid receptors with a higher affinity for the μ receptor. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release.

Tramadol has an antitussive effect. In contrast to morphine, analgesic doses of tramadol over a wide range have no respiratory depressant effect. Also, gastrointestinal motility is less affected. Effects on the cardiovascular system tend to be slight. The potency of tramadol is reported to be 1/10 to 1/6 that of morphine.

5.2 Pharmacokinetic properties

Tramadol is readily absorbed after oral doses but is subject to some first-pass metabolism. Mean absolute bioavailability is about 70 to 75% after oral use and 100% after intramuscular injection. Plasma protein binding is about 20%. Tramadol is metabolised by *N*- and *O*-demethylation via the cytochrome P450 isoenzymes CYP3A4 and CYP2D6 and glucuronidation or sulfation in the liver. The metabolite *O*-desmethyltramadol is pharmacologically active. Tramadol is excreted mainly in the urine, predominantly as metabolites.

Tramadol is widely distributed, crosses the placenta, and appears in small amounts in breast milk. The elimination half-life is about 6 hours.

5.3 Preclinical safety data

On repeated oral and parenteral administration of tramadol for 6 - 26 weeks in rats and dogs and oral administration for 12 months in dogs, haematological, clinico-chemical and histological investigations showed no evidence of any substance-related changes. Central nervous manifestations only occurred after high doses considerably above the therapeutic range: restlessness, salivation, convulsions, and reduced weight gain. Rats and dogs tolerated oral doses of 20 mg/kg and 10 mg/kg body weight respectively, and dogs rectal doses of 20 mg/kg body weight without any reactions.

In rats, tramadol dosages from 50 mg/kg/day upwards caused toxic effects in dams and raised neonate mortality. In the offspring retardation occurred in the form of ossification disorders and delayed vaginal and eye opening. Male fertility in rats was not affected. After higher doses (from 50 mg/kg/day upwards) females exhibited a reduced pregnancy rate. In rabbits there were toxic effects in dams from 125 mg/kg upwards and skeletal anomalies in the offspring.

In some in vitro test systems there was evidence of mutagenic effects. In vivo studies showed no such effects.

According to knowledge gained so far, tramadol can be classified as non-mutagenic.

Studies on the tumorigenic potential of tramadol hydrochloride have been carried out in rats and mice. The study in rats showed no evidence of any substance-related increase in the incidence of tumours. In the study in mice there was an increased incidence of liver cell adenomas in male animals (a dose-dependent, non-significant increase from 15mg/kg upwards) and an increase in pulmonary tumours in females of all dosage groups (significant, but not dose-dependent).

6.1 List of Excipients

Sodium Acetate Anhydrous BP

Disodium Edetate BP

Water for Injection BP

6.2 Incompatibilities: Not applicable.

6.3 Shelf life: 24months.

6.4 Special precautions for storage

Store in cool place below 30°C. Protect from light. Do not Freeze. Keep out of reach of Children.

6.5 Nature and contents of container

2 ml Ampoules (2 × 5 × 2 ml Ampoules)

6.6 Special precautions for disposal and other handling

No special requirements.

**7.MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE
ADDRESSES MARKETING AUTHORISATION HOLD**

Cachet Pharmaceuticals Private

Limited Address: 415, Shah Nahar

Ind. Estate,

Dr. E. Moses Road,

Worli, Mumbai-400

018 Maharashtra,

India

Telephone: +91-22-24970011 / +91-22-40829999

MANUFACTURING SITE ADDRESSES:

Sakar Healthcare Ltd

Block No. 10-13, Sarkhej-Bavla
Highway, Vill: Changodar, Dist:
Ahmedabad-382213, Gujarat – INDIA.
Phone :+91-02717 250477

Fax :+91-02717 251621

E.mail :
info@sakarhealthcare.com

Website:
www.sakarhealthcare.com

8.MARKETING AUTHORISATION NUMBER

H2025/CTD12466/26712

9.DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

-Not applicable.

10. DATE OF REVISION OF THE TEXT

20/08/2026.