Insert Leaflet

Trama Injection
Solution for Injection

Composition
Active substance
Each 2 ml ampoule contains 100 mg tramadol hydrochloride.

Inactive substances
Sodium acetate, water for injection.

Therapeutic class: Centrally acting opioid analgesic

Indications
Moderate to severe pain

Posology and method of administration
The injection is for parenteral administration either intramuscularly, by slow intravenous injection or, when diluted in solution, by infusion or patient controlled analgesia. As with all analgesic drugs the dosing of Trama Injection should be adjusted depending on the severity of the pain and the individual clinical response of the patient.

Adults: A single dose of 50 or 100 mg 4-6 hourly (1 or 2 mL of Trama injection) is usually required.

Intravenous injections must be given slowly over 2-3 minutes.

For severe (post-operative) pain, administer an initial bolus of 100 mg. during the 60 minutes following the initial bolus, further doses of 50 mg may be given every 10-20 minutes, up to a total dose of 250 mg including the initial bolus.

Subsequent doses should be 50 or 100 mg administered 4-6 hourly.

If the administration of Trama injection has been forgotten, the pain may be return. The dose should not be doubled. Administration should be continued as before.

A total daily dose of 400 mg should not be exceeded except in special clinical circumstances.

Trama 100 mg, solution for injection is injected into the veins (usually into a blood vessel under the surface of the arm), muscles (usually the buttocks) or under the skin.
Administration into the veins is slow with 1 ml Trama 100 mg, solution for injection (equivalent to 50 mg tramadol hydrochloride) per minute.
Alternatively Trama injection may be diluted with a suitable infusion solution (e.g. 0.9% physiological saline or 5% glucose solution) for i.v. infusion or for patient-controlled analgesia (PCA).

Elderly patients: Dosing as for adults but it should be noted that in a study in elderly volunteers (aged over 75 years) the elimination half-life for orally administered tramadol was increased by 17%.

Patients with renal insufficiency/renal dialysis: As the elimination of tramadol may be prolonged in patients with renal impairment, the usual initial adult doses should be employed, but prolongation of the dosage interval should be carefully considered according to the patient's requirements.

For creatinine clearance <30 ml/min the dosing should be increased to 12 hourly intervals.
For creatinine clearance <10 ml/min (severe renal impairment) tramadol is not recommended.

Tramadol is removed very slowly by haemodialysis or haemofiltration and therefore post dialysis dosing to maintain analgesia is usually unnecessary.

Patients with hepatic insufficiency: It should be noted that as the elimination of tramadol may be prolonged in severe hepatic impairment, although the usual initial adult doses should be used, prolongation of the dosing should be at 12 hourly intervals.

Children: Over 14 years: Dosage as for adults.

Children aged 1 to 14 years receive 1-2 mg tramadol hydrochloride per kg body weight as a single dose.
In this case Trama solution for injection is diluted in water for injection, the following table shows which concentrations are achieved (1 ml Trama 100 solution for injection contains 50 mg tramadol hydrochloride):

Diluting Trama solution for injection

In water for Injections	Gives the following concentrations	In water for Injections	Gives the following concentrations
2 ml+2 ml	25.0 mg/ml	2 ml+12 ml	7.1 mg/ml
2 ml+4 ml	16.7 mg/ml	2 ml+14 ml	6.3 mg/ml
2 ml+6 ml	12.5 mg/ml	2 ml+16 ml	5.6 mg/ml
2 ml+8 ml	10.0 mg/ml	2 ml+18 ml	5.0 mg/ml
2 ml+10 ml	8.3 mg/ml		

Example: the doctor would like to give 1.5 mg tramadol hydrochloride per kg body weight to a child weighing 45 kg. This requires 67.5 mg tramadol hydrochloride. Therefore 2 ml Trama solution for injection are diluted in 4 ml water for injection. This results in a concentration of 16.7 mg tramadol hydrochloride per ml. 4 ml (approx. 67 mg tramadol hydrochloride) of the diluted solution are then administered.

If you interrupt or stop treatment with Trama injection too soon, pain is likely to return.
In general stopping treatment with Trama injection will have no after-effects. However, in some patients given Trama injection for a very long time and then stopped suddenly, after-effects may occur. The patients might feel restless, anxious or nervous. They might be overactive, sleep badly, or have stomach or bowel trouble. A very small number of people might have panic attacks, hallucinations, abnormal sensations such as tingling and numbness, or ringing in the ears (tinnitus).

Contra-indications
Trama Injection should not be given to patients who have previously shown hypersensitivity to tramadol or any of the excipients.
The product should not be administered to patients suffering from acute intoxication with hypnotics, centrally acting analgesics, opioids, psychotropic drugs or alcohol.
In common with other opioid analgesics, tramadol should not be administered to patients who are receiving monoamine oxidase (MAO) inhibitors or within 2 weeks of their withdrawal.
The product must not be used in epilepsy not adequately controlled by treatment.

Special warnings and precautions for use
Warnings: At therapeutic doses, tramadol has the potential to cause withdrawal symptoms.
Rarely cases of dependence and abuse have been reported.
Because of this potential the clinical need for continued analgesic treatment should be reviewed regularly.

In patients with a tendency to drug or alcohol abuse or dependence, treatment should be for short periods and under strict medical supervision, because in these cases there is a risk of suicidal tendency.

Trama Injection is not a suitable substitute in opioid dependent patients. The product does not suppress morphine withdrawal symptoms although it is an opioid agonist.

Convulsions have been reported at therapeutic doses and the risk may be increased at doses exceeding the usual upper daily dose limit (400 mg tramadol). Patients with a history of epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling reasons. The risk of convulsions may increase in patients taking tramadol and concomitant medication that can lower the seizure threshold (*see Interactions section*).

Precautions
In patients with severe renal or hepatic impairment, head injury, increased intracranial pressure, or patients in shock or at risk of convulsions, Trama Injection should be used with caution.
At present Trama Injection should not be used during light planes of anaesthesia as enhanced intra-operative recall was reported in a study of the use of tramadol during anaesthesia with enflurane and nitrous oxide.

At therapeutic doses of tramadol respiratory depression has been reported infrequently. Therefore care should be taken when administering Trama Injection to patients with existing respiratory depression or to patients taking concomitant CNS depressant drugs.
Trama injection contains sodium, but less than 1 mmol (23 mg) sodium per ampoule, i.e., it is almost "sodium-free".

Interaction with other medical products and other forms of interaction
Trama Injection may potentiate the CNS depressant effects of other centrally acting drugs (including alcohol, sedatives, sleeping pills and certain pain killers such as morphine and codeine) when administered concomitantly with such drugs. The patient may feel dazed or that he is going to faint.

Tramadol may increase the potential for both selective serotonin re-uptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) to cause convulsions (See Special Warnings and Precautions for Use and Pharmacokinetic Properties sections).
Isolated cases of serotonin syndrome have been reported in temporal connection with concomitant use of tramadol and selective serotonin re-uptake inhibitors (SSRI) and MAO inhibitors. Symptoms of serotonin syndrome are, for example, confusion, restlessness, high temperature, sweating, uncoordinated movements of the limbs or eyes, uncontrollable muscle twitching or diarrhea.

Increased INR and ecchymoses have been reported during concomitant treatment with tramadol and coumarin derivatives.

Administration of Trama Injection together with carbamazepine, pentazocine, nalbuphine or buprenorphine (painkillers), ondansetron (for nausea) results in markedly decreased serum concentrations of tramadol which may reduce analgesic effectiveness and shorten the duration of action.

Changes in serum concentrations of tramadol have been associated with simultaneous dosing of cimetidine. However, such changes are clinically insignificant and therefore no dosage adjustment for Trama Injection is recommended in patients receiving chronic cimetidine therapy.

Inhibitors of CYP3A4 (e.g. ketoconazole or erythromycin) may inhibit the tramadol metabolism.

The action on blood clotting of coumarin anticoagulants, for example warfarin, may be affected while taking them with Trama injection, and bleeding may occur.

Pregnancy and lactation
Pregnancy: Sufficient evidence of the safety of tramadol during pregnancy in humans is not available. Therefore you should not use Trama injection throughout pregnancy. The repeated use of Trama injection during pregnancy may lead to habituation in the unborn child and as a result, the child may experience withdrawal symptoms after birth.

Lactation: Trama Injection should not be administered during breast feeding. Tramadol is excreted in very small amounts into the breast milk. After a single administration of tramadol it is not usually necessary to stop breast-feeding.

Effects on ability to drive and use machines
Trama Injection may lead to dizziness, muzziness and blurred vision and therefore affect the patient's reactions. Patients should be warned not to drive a car or another vehicle, not to use electric tools or operate machinery and not to work without a firm hold, if affected.

Undesirable effects
The most commonly reported adverse reactions are nausea and dizziness.
Common effects were headache, muzziness, constipation, dry mouth, vomiting and sweating.
Uncommon effects include disorders of cardiovascular regulation (e.g. palpitation, tachycardia, postural hypotension up to cardiovascular collapse), further, retching and gastrointestinal irritation, or dermal reactions (e.g. pruritus, rash or urticaria).
Rarely reported effects include bradycardia, muscle twitching, coordination disorders, temporary loss of consciousness, syncope, increase in blood pressure, change in appetite, paraesthesia, tremor, hallucinations, confusion, sleep disorders and nightmares, changes in mood (usually elation, occasionally dysphoria), change in activity, change in cognitive and sensorial capacity (e.g. perception disorders), breathlessness (dyspnoea). Rare effects are also motorial weakness, blurred vision and micturition disorders. In a few isolated cases an increase in liver enzyme values has been reported in a temporal connection with the therapeutic use of tramadol.

Respiratory depression has been reported. Convulsions have been reported rarely *(see Interactions section).*
Dependence, abuse and withdrawal reactions have been reported (*see Posology and Method of Administration and Special Warnings and Precautions for Use sections*).
If treatment is discontinued abruptly, typical opiate withdrawal reactions include agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastro-intestinal symptoms may occur; very rarely panic attacks, severe anxiety, paraesthesias, tinnitus and unusual CNS symptoms have been reported.

There have been rare cases of blood dyscrasias observed with tramadol treatment but direct causality has not been confirmed.

Allergy to tramadol is characterized by dyspnoea, wheezing, bronchospasm, worsening of existing asthma, angioneurotic oedema and anaphylaxis.

Overdose
Accidental administration of an additional dose of Trama injection usually has no negative effects. The next dose should be given as planned.
After administration very high doses, pin-point pupils, vomiting, fall in blood pressure, fast heart-beat, feeling faint, reduced level of consciousness up to coma (deep unconsciousness), epileptic-like fits, and difficulty in breathing up to stoppage of breathing may occur.

Treatment of overdose requires the maintenance of the airway and cardiovascular functions. Respiratory depression may be reversed using naloxone and fits controlled with diazepam.

The treatment of acute overdose of tramadol using haemodialysis or haemofiltration alone is not sufficient or suitable due to the slow elimination of tramadol from the serum by these routes.

Pharmacological properties
Pharmacodynamic properties: Tramadol, a cyclohexanol derivative, is a centrally acting analgesic, which possesses opioid agonist properties. Tramadol appears to modify the transmission of pain impulses by inhibition of monoamine reuptake. The analgesic activity of tramadol has been demonstrated in both animal models and human subjects.
Tramadol also has an antitussive action but has no effect on gastrointestinal motility. At the recommended dosages, the effects of tramadol given parenterally on the respiratory and cardiovascular systems appear to be clinically insignificant.

Pharmacokinetic properties: General: The mean absolute bioavailability after intramuscular administration was found to be 100%.
The distribution of tramadol following intravenous administration is rapid and in two phases with different half-lives of 0.31 ± 0.17 hours (initial rapid phase) and 1.7 ± 0.4 hours (slower phase) respectively.
After intravenous administration of 100 mg tramadol, the serum concentration was 613 ± 221 ng/ml at 15 minutes post dosing and 409 ± 79 ng/ml at 2 hours post dosing. Tramadol has a high tissue affinity with an apparent volume of distribution of 203 L after intravenous dosing in healthy volunteers.
Tramadol undergoes hepatic metabolism with approximately 85% of an intravenous dose being metabolised in young healthy volunteers. Tramadol is biotransformed primarily by N- and O-demethylation and by glucuronidation of the O-demethylation products. Eleven metabolites have so far been identified in man. Only one metabolite, O-demethyl tramadol (M1), is pharmacologically active showing analgesic activity.
Tramadol is essentially excreted via the kidneys. The mean elimination half-life of tramadol following intravenous administration is 5-6 hours. Total clearance of tramadol was 28.0 L/h following intravenous administration.

Characteristics in patients: Effect of age: Tramadol pharmacokinetics show little age-dependence in volunteers up to the age of 75 years. In volunteers aged over 75 years, the terminal elimination half-life was 7.0 ± 1.6 h compared to 6.0 ± 1.5 h in young volunteers after oral administration.

Effect of hepatic or renal impairment: As both tramadol and its pharmacologically active metabolite, O-desmethyl tramadol, are eliminated both metabolically and renally, the terminal half-life of elimination (t½) may be prolonged in patients with hepatic or renal dysfunction. However, the increase in t½ is relatively small if either excretory organ is functioning normally. In liver cirrhosis patients, the mean t½ of tramadol was 13.3 ± 4.9 hours. In patients with renal failure (creatinine clearance < 5 mL/min) the t½ of tramadol was 11.0 ± 3.2 hours and that of M1 was 16.9 ± 3.0 hours. Extreme values observed to date are 22.3 hours (tramadol) and 36.0 hours (M1) in liver cirrhosis patients and 19.5 hours (tramadol) and 43.2 hours (M1) in renal failure patients.

Preclinical safety data: The standard range of pharmacodynamic, pharmacological and toxicological tests have been carried out for tramadol and the effects observed from these investigations that are relevant to the prescriber are mentioned in other sections.

Presentation and Contents
Solution for injection in packs of 5 ampoules.

Storage condition: store below 25ºC.
License No: 1467733381

Manufacturer: Rafa Laboratories Ltd. P.O.B. 405, Jerusalem 91003

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in October 2011.