**TRAMADOL 100 MG ROTEXMEDICA**
**Solution for injection.**

## COMPOSITION

Tramadol 100 mg Rotexmedica solution for injection: 1 ampoule of 2 ml contains 100 mg tramadol hydrochloride

Other ingredients: Sodium acetate and water for injections.

## CLINICAL PARTICULARS

### Therapeutic Indications

Moderate to severe pain.

### Pharmacotherapeutic Group -

Centrally acting opioid analgesic. Tramadol: N02AX02

### Dosage 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 Tramadol Rotexmedica solution for 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 mg or 100 mg 4-6 hourly (1 or 2 ml of Tramadol Rotexmedica solution for injection) is usually required.

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

For severe (postoperative) 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 to 20 minutes, up to a total dose of 250 mg including the initial bolus.

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

If the administration of Tramadol Rotexmedica solution for injection has been forgotten, the pain may 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.

Tramadol Rotexmedica solution for injection is injected into the veins (usually into blood vessels under the surface of the arms), muscle (usually the buttocks) or under the skin.

Administration into the veins is slow, with 1 ml Tramadol Rotexmedica solution for injection (equivalent to 50 mg tramadol hydrochloride)/minute.

Alternatively Tramadol Rotexmedica solution for injection may be diluted with a suitable infusion solution (0.9% physiological saline or 5% glucose solution) for I.V. infusion or for patient-controlled analgesia (PCA).

***Elderly Use:*** in subjects over the age of 75 years, serum concentrations are slightly elevated and the elimination half-life is slightly prolonged. Subjects in this age group are also expected to vary more widely in their ability to tolerate adverse drug effects. Daily doses as for adults but should not exceed 300 mg.

***Patients with renal insufficiency/dialysis:*** as 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 patient's requirements.

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

Tramadol is removed very slowly by hemodialysis or hemofiltration 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 dose should be used, prolongation of the dosing should be at 12-hour intervals.

***Paediatric Use:*** Over 14 years, dosage as for adults.

**Children aged 1 year to 14 years** receive 1-2 mg tramadol/kg body weight as a single dose. See table referring to the concentration of tramadol obtained by dilution in water accordingly:

| 100 mg (2 ml) of tramadol diluted in number of ml water | Obtained Concentration of tramadol |
|---|---|
| 2 ml water | 25.0 mg/1 ml |
| 4 ml water | 16.7 mg/1 ml |
| 6 ml water | 12.5 mg/1 ml |
| 8 ml water | 10.0 mg/1 ml |
| 10 ml water | 8.3 mg/1 ml |
| 12 ml water | 7.1 mg/1 ml |
| 14 ml water | 6.3 mg/1 ml |
| 16 ml water | 5.6 mg/1 ml |
| 18 ml water | 5.0 mg/1 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 Tramadol Rotexmedica 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 Tramadol Rotexmedica solution for injection too soon, pain is likely to return.

In general ceasing treatment with the drug will not cause any after effects. However, in some patients given Tramadol Rotexmedica solution for injection for a very long time and then abrupt 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).

### Contraindications

Tramadol Rotexmedica solution for injection should not be given to patients who have previously known 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 drug must not be used in epilepsy not adequately controlled by treatment.

### Special Warnings and Precautions

***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.

Tramadol Rotexmedica solution for 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).

***Precautions:*** In patients with severe renal or hepatic impairment, head injury, increased intracranial pressure, or patients in shock or at risk of convulsions, Tramadol Rotexmedica solution for injection should be used with caution.

At present, Tramadol Rotexmedica solution for 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 dose of tramadol respiratory depression has been reported infrequently. Therefore care should be taken when administering Tramadol Rotexmedica solution for injection to patients with existing respiratory depression or to patients taking concomitant CNS depressant drugs.

Tramadol Rotexmedica solution for injection contains sodium, less than 1mmol (23 mg) sodium/ampoule, almost declared as "sodium free".

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

Tramadol Rotexmedica solution for 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 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 eye, uncontrollable muscle twitching or diarrhoea.

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

Administration of Tramadol Rotexmedica solution for injection together with carbamazepine, pentazocine, nalbuphine or buprenorphine (pain killers), ondansetron (for nausea) results in markedly decreased serum concentration 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 Tramadol Rotexmedica solution for injection is recommended in patients receiving chronic cimetidine therapy.

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

The action on blood clotting of Coumadin anticoagulants, for example warfarin, may be affected while taking them with Tramadol Rotexmedica solution for injection and bleeding may occur.

### Pregnancy and Lactation

***Pregnancy:*** Sufficient evidence of the safety of tramadol during pregnancy in humans is not available. Therefore, Tramadol Rotexmedica solution for injection should not be used in pregnancy. The repeated use of Tramadol Rotexmedica solution for injection during pregnancy may lead to habituation in the unborn child and as a result, the child may experience withdrawal symptoms after birth.

***Lactation:*** Tramadol Rotexmedica solution for injection should not be administered during breastfeeding. Tramadol is excreted in very small amounts into the breast milk. After a single administration of tramadol it is not usually necessary to stop breastfeeding.

**Effects on Ability to Drive and Use Machines**

Tramadol Rotexmedica solution for injection may cause 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 drug reactions are nausea and dizziness.

***Common*** effects were headache, muzziness, constipation, dry mouth, vomiting and sweating.

***Uncommon*** effects include disorders of cardiovascular regulation (palpitation, tachycardia, postural hypotension up to cardiovascular collapse). Further, retching and gastrointestinal irritation, or dermal reaction (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, paresthesia, tremor, hallucinations, confusions, sleep disorders and nightmares, change in mood (usually elation, occasionally dysphoria), change in activity, change in cognitivity and sensorial capacity (perception disorders), breathlessness (dyspnea). Rare effects are also motoric weakness, blurring vision and micturition disorders. In a few isolation cases an increase in liver enzyme value 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).

Dependence, abuse and withdrawal reaction have been reported (see Dosage and Method of Administration & Special Warnings and Precautions sections).

If treatment is discontinued abruptly, typical opiate withdrawal reactions include agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms may occur; very rarely panic attacks, severe anxiety, paresthesia, 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 edema and anaphylaxis.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il).

**Overdose**

Accidental administration of an additional dose of Tramadol Rotexmedica solution for injection usually has no negative effects. The next dose should be given as planned.

After administration of 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 hemodialysis or hemofiltration alone is not sufficient or suitable due to the slow elimination from the serum by these routes.

Symptoms of overdosage are typical of other opioid analgesics, and include myosis, vomiting, cardiovascular collapse, sedation and coma, seizures and respiratory depression.

## PHARMACOLOGICAL PROPERTIES

**Pharmacodynamic Properties**

Tramadol Rotexmedica solution for injection is a centrally acting analgesic. It is a non selective pure agonist at mu, delta and kappa opioid receptors with a higher affinity for the mu receptor. Other mechanisms which may 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, tramadol in analgesic doses has no respiratory depression effect over a wide range and no effect on gastrointestinal motility. It has only a slight effect on the cardiovascular system. Tramadol potency is given as 1/10 to 1/6 of that for morphine.

**Pharmacokinetic Properties**

Following oral use tramadol absorption is greater than 90%. Absolute average bioavailability is 70%, irrespective of concurrent food intake. The difference between available absorbed and unmetabolized tramadol can be explained by the fact that there is only slight first-pass metabolism. First-pass metabolism following oral administration is 30% at most.

Following oral use (100 mg) in liquid form, peak plasma concentrations ($C_{max}$) after 1.2 hours are calculated to be 309 ± 90 ng/ml and following a similar dose in solid oral form peak plasma concentrations ($C_{max}$) after 2 hours are 280 ± 49 ng/ml. Tramadol has high tissue affinity (Vd,$\beta$ = 203 ± 40 l). Serum protein binding is approximately 20%.

Tramadol crosses the blood-brain barrier and the placenta. Very slight amounts of the drug together with its O-desmethyl derivate are found in maternal milk (0.1% and 0.02% of the administrated dose, respectively).

The elimination half-life ($t_{1/2\beta}$) is about 6 hours, irrespective of the method of administration. In patients over 75 years of age, elimination half-life may be prolonged by a factor of approx. 1.4.

In humans tramadol is essentially metabolized by N- and O-demethylation as well as by conjugation of the O-demethylation products with glucuronic acid. Only O-desmethyl tramadol is pharmacologically active. There are considerable quantitative interindividual variations as regards the other metabolites. 11 metabolites have been found in urine to date. According to results of animal experiments, O-desmethyl tramadol exceeds the potency of the parent substance by a factor of 2 to 4. Its half-life ($t_{1/2\beta}$) (6 healthy volunteers) is 7.9 hours (ranging between 5.4 to 9.6 hours) and is similar to that of tramadol.

Inhibition of the isoenzymes CYP3A4 and/or CYP2D6 involved in the biotransformation of tramadol can influence the plasma concentration of tramadol or that of its active metabolites. No clinically relevant interactions have been reported to date.

Tramadol and its metabolites are almost completely excreted via the kidneys. Cumulative urinary excretion is 90% of the total radioactivity of the administered dose. Tramadol half-life may be slightly prolonged in patients with impaired liver or kidney function. Elimination half-lives of 13.3 ± 4.9 hours (tramadol) and of 18.5 ± 9.4 hours (O-desmethyl tramadol) and in extreme cases of 22.3 and 36 hours respectively have been determined in patients with cirrhosis of the liver. Elimination half-lives of 11 ± 3.2 hours and 16.9 ± 3 hours, and in extreme cases of 19.5 hours and 43.2 hours, respectively have been determined in patients with renal insufficiency (creatinine clearance < 5 ml/min).

Tramadol at therapeutic doses shows a linear pharmacokinetic profile.

The relation between serum concentrations and analgesic effect is dose-dependent, while showing significant individual variations. As a rule, serum concentrations of 100-300 ng/ml are effective.

**Preclinical Safety Data**

Some *in vitro* test systems have indicated mutagenic effects. *In vivo* tests have given no indications of mutagenic effects. According to current knowledge, tramadol can be classified as a non-mutagenic substance.

Studies on the tumorigenic potential of tramadol hydrochloride have been carried out in the rat and mouse. The rat study gave no indications of substance-related increases in tumour incidence. In the mouse study, increased incidence of liver cell adenoma was observed in the males (dose-dependent, non-significant increases from 15 mg/kg) and an increase in lung tumours in the females of all dose groups (significant but non-dose-dependent increases).

In studies on reproduction toxicity tramadol dosages from 50 mg/kg/day in the rat produced maternal toxic effects and led to increased neonate mortality. Delayed growth in the form of disorders of ossification and delayed vaginal and eye opening occurred in the progeny. Teratogenic effects were not observed. The fertility of male rats was not impaired. Females on high doses (from 50 mg/kg/day) showed a reduced gestation index. From 125 mg/kg maternal toxic effects occurred in rabbits as well as skeletal anomalies in the progeny.

## PHARMACEUTICAL PARTICULARS

**List of Excipients**

Sodium acetate, Water for injections.

**Incompatibilities**

Tramadol Rotexmedica solution for injection is incompatible with injection solutions of: Diclofenac, Diltiazem, Flunitrazepam, Glycerol trinitrate, Indometacin, Midazolam, Phenyl butazone.

**Shelf Life**

Shelf life in an intact ampoule is three years.

The shelf life after dilution with sodium chloride solution 0.9% and glucose solution 5% is 24 hours if stored below 30°C.

The dilution should be prepared immediately before administration.

**Special Precautions for Storage**

Store below 30°C, protect from light.

Any portion of the contents remaining after opening should be discarded.

**Presentations**

Each carton contains ten glass ampoules (type I):

2 ml vial: 100 mg tramadol hydrochloride

**Manufacturer**

Rotexmedica GMBH

BUNSENSTRASSE 4 · D-22946 TRITTAU/GERMANY

**Importer & License Holder**

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