SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

1.1 Brand Name	**:**	**TRADMIN**
1.2 Generic Name	**:**	Tramadol Injection BP
1.3 Strength	**:**	50 mg/ml
1.4 Pharmaceutical Form	**:**	Liquid Injection

2. QUALITY AND QUANTITATIVE COMPOSITION

Each ml contains:

Tramadol Hydrochloride BP……... 50mg

Water for Injections BP……...q.s.

3. PHARMACEUTICAL FORM VISUAL DESCRIPTION:

Clear, colourless liquid filled in clear transparent glass ampoule.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS:

For the treatment and prevention of moderate to severe pain.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

The tramadol solution is for parenteral injection either intramuscularly, by slow intravenous injection or diluted in solution for administration by infusion or patient controlled analgesia.

Adults and children 12 years and over

The usual dose is 50mg or 100mg, 4 to 6 hourly by either intramuscular or intravenous routes. Intravenous injections must be given slowly over 2-3 minutes. The dose should be adjusted accordingly to the severity of the pain and the response.

For post-operative pain, an initial bolus of 100 mg is administered. During the 60 minutes following the initial bolus, further doses of 50mg may be given every 10-20 minutes, up to a total dose of 250mg including the initial bolus. Subsequent doses should be 50mg or 100mg 4-6 hourly up to a total daily dose of 600mg.

Children under 12 years

Not recommended.

4.3 CONTRAINDICATIONS

Tramadol 50mg/ml solution for injection should not be given to patients who have previously demonstrated hypersensitivity towards tramadol or any of the other ingredients. Tramadol 50mg/ml Solution for Injection should not be given to patients suffering from acute intoxication with alcohol, hypnotic, centrally acting analgesics, opioid or psychotropic drugs.

In common with other opioid analgesics, tramadol should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal.

Tramadol 50mg/ml Solution for Injection is contraindicated in patients with epilepsy not adequately controlled by treatment.

Tramadol must not be used in narcotic withdrawal treatment.

4.4 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.

At therapeutic doses withdrawal symptoms have been reported at a frequency of 1 in 8000. Reports of dependence and abuse have been less frequent. Because of this potential the clinical need for continued analgesic treatment should be reviewed regularly.

Tramadol has a low dependence potential. On long term use tolerance, psychic and physical dependence may develop. In patients with a tendency to drug abuse or dependence, treatment should be for short periods and under strict medical supervision.

Tramadol 50mg/ml Solution for injection is not a suitable substitute in opioid dependent patients. The product does not supress morphine withdrawal symptoms although it is an opioid agonist.

Tramadol 50mg/ml Solution for Injection may cause drowsiness and this effect may be potentiated by alcohol and other CNS depressants. Ambulant patients should be warned not to drive or operate machinery if affected.

Precautions

Tramadol 50mg/ml Solution for Injection should be used with caution in opioid-dependent patients, patients with head injury, a reduced level of consciousness of uncertain origin, disorder of the respiratory centre or function, increased intracranial pressure, severe impairment of hepatic and renal function and in patients prone to convulsive disorders or in shock. In patients sensitive to opiates the product should only be used with caution.

Convulsions have been reported at therapeutic doses and the risk may be increased at doses exceeding the usual upper daily dose limit. 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.

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. At therapeutic doses respiratory depression has infrequently been reported.

4.5 INTERATION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS

Tramadol 50mg/ml Solution for Injection should not be combined with MAO inhibitors.

In patients treated with MAO inhibitors in the 14 days prior to the use of the opioid pethidine, life-threatening interactions on 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 50mg/ml Solution for Injection.

The combination with mixed agonist/ antagonists (e.g. buprenorphine, nalbuphine, pentazocine) and tramadol is not advisable, because the analgesic effect of a pure agonist may be theoretically reduced in such circumstances.

Concomitant administration of Tramadol 50mg/ml Solution for Injection with other centrally acting drugs, including alcohol, may potentiate CNS depressant 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.

Theoretically there is a possibility that tramadol could interact with lithium. There have been no reports of this potential interaction. Concomitant therapeutic use of tramadol and 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°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.

There have been isolated reports of interaction with coumarin anticoagulants resulting in an increased INR with major bleeding and ecchymoses in some patients and so care should be taken when commencing treatment with tramadol in patients on anticoagulants.

Pharmacokinetic studies were conducted to investigate the effects of cimetidine, quinidine and carbamazepine on the pharmacokinetics of tramadol.

Carbamazepine- The simultaneous administration of carbamazepine markedly decreases serum concentrations of tramadol to an extent that a decrease in analgesic effectiveness and a shorter duration of action may occur. *Cimetidine*- With the concomitant or previous administration of cimetidine clinically relevant interactions are unlikely to occur. Therefore, no alteration of the tramadol dosage regimen is recommended for patients receiving chronic cimetidine therapy.
Quinidine- A study in 12 healthy volunteers has shown that quinidine causes an approximate 25% increase in the tramadol Cmax and AUC; Tmax is unaffected. However, the increases in Cmax and AUC fall within the normal therapeutic range for tramadol, and no dosage adjustment is required.
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.
In a limited number of studies, the pre- or postoperative application of the antiemetic 5-HT3 antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain.

4.6 PREGNANCY AND LACTATION

Pregnancy

Animal studies with tramadol at very high doses have revealed effects on organ development, ossification and neonatal mortality. Teratogenic effects were not observed. Tramadol crosses the placenta. There is inadequate evidence available on the safety of tramadol in human pregnancy, therefore Tramadol 50mg/ml Solution for Injection should not be used in pregnant women. Tramadol-administered before a during birth-does not affect uterine contractility. In neonates it may induce changes in the respiratory rate which are usually not clinically relevant. Chronic use during pregnancy may lead to neonatal withdrawal symptoms.

Breastfeeding

Tramadol and its metabolites are found in small amounts in human breast milk. An infant could ingest 0.1% of the dose given to the mother. Tramadol 50mg/ml Solution for Injection should not be administered during breastfeeding. After a single administration of tramadol however, it is not usually necessary to interrupt breast feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

Tramadol 50mg/ml Solution for Injection may cause somnolence and dizziness and these effects may be potentiated by alcohol and other CNS depressants. Ambulant patients should be warned not to drive or operate machinery if affected.

4.8 UNDESIRABLE EFFECTS

Dizziness, Nausea, Sweating, Fatigue, Vomiting, Constipation, Dry mouth.

4.9 OVERDOSAGE

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

In case of intoxication orally, gastrointestinal decontamination with activated charcoal or by gastric lavage is only recommended within 2 hours after tramadol intake. Gastrointestinal decontamination at a later time point may be useful in case of intoxication with exceptionally large quantities.

Tramadol is minimally eliminated from the serum by haemodialysis or haemo-filtration. Therefore, treatment of acute tramadol intoxication with haemodialysis or hemofiltration alone is not suitable for detoxification.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMICS PROPERTIES

Tramadol, a centrally-acting analgesic, exists as a racemic mixture of the *trans* isomer, with important differences in binding, activity and metabolism associated with the two enantiomers. It is 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 od noradrenaline and enhancement of serotonin release.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

More than 90% of tramadol is absorbed after oral administration. The mean absolute bioavailability is approximately 70%, irrespective of the concomitant intake of food. The difference between absorbed and non-metabolised available tramadol is probably due to the low first-pass effect. The first-pass effect after oral administration is a maximum of 30%.

Distribution

Tramadol has a high tissue affinity ($V_{d\beta}$ = 203 ± 40I). It has a plasma protein binding of about 20%.

Metabolism

Hepatic. The major metabolic pathways appear to be N- and O-demethylation and glucuronidation or sulfation in the liver. One metabolite (O-desmethyltramadol, denoted M1) is pharmacologically active in

animal models. CYP3A4 and CYP2B6 facilitates the biotransformation of tramadol to N-desmethyl tramadol. CYP2D6 facilitated the biotransformation of tramadol to O-desmethyl- tramadol.

Elimination

Tramadol is eliminated primarily through metabolism by the liver and the metabolites are excreted primarily by the kidneys.

5.3 PRECLINICAL SAFETY DATA

Not Applicable

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium Acetate Trihydrate BP, Water for Injections BP.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

24 Months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30 ºC. Protect from light & moisture. Do not Freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

Tray of 5 x 2 ml ampoules packed in mono-cartons along with pack inserts.

6.6 SPECIAL PRECAUTION FOR DISPOSAL

Not Applicable

7. MARKETING AUTHORIZATION HOLDER

Name : **UNOSOURCE PHARMA LTD.**

Address : 503/504, 5th floor, Hubtown Solaris, N.S. Phadke Marg, Andheri- East, Mumbai- 400069, INDIA

Phone: +91 22 61056105

8. MARKETING AUTHORIZATION NUMBERS

We will submit after registration.

9. REGISTRATION DETAILS

We will submit after registration.

10. DATE OF REVISION OF THE TEXT

NA

11. NAME AND ADDRESS OF THE MANUFACTURE

Name	:	AKUMS DRUGS & PHARMACEUTICALS LTD.
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