SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

1.1 Brand Name : TRADMIN

1.2 Generic Name : Tramadol Capsules BP

1.3 Strength : 50 mg

1.4 Pharmaceutical Form: Capsule

2. QUALITY AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains:

Tramadol Hydrochloride BP...…….50 mg

3. PHARMACEUTICAL FORM VISUAL DESCRIPTION:

Green/Green coloured, size '2' hard gelatin capsules containing white granular powder.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS:

Management (treatment and prevention) of moderate to severe pain.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

As with all analgesic drugs, the dose of tramadol should be adjusted according to the severity of the pain and the clinical response of the individual patient.

Adults and children aged 12 years and over:

Acute pain: An initial dose of 100 mg is usually necessary, followed by 50 mg or 100 mg not more frequently than 4 hourly. The duration of therapy should be matched to clinical need. **Pain associated with chronic conditions:** Use an initial dose of 50 mg and then titrate the dose according to the severity of the pain.

The need for continued treatment should be assessed at regular intervals as withdrawal symptoms and dependence have been reported. A total daily dose of 400 mg should not be exceeded except in special clinical circumstances.

Children under 12 years: Not recommended.

Elderly: The usual dosages may be used although it should be noted that in volunteers aged over 75 years the elimination half-life of tramadol was increased by 17 % following oral administration.

Renal impairment/renal dialysis: The elimination of tramadol may be prolonged. The usual initial dosage should be used. For patients with creatinine clearance less than 30 ml per minute, the dosage interval should be increased to 12 hours. Tramadol is not recommended for patients with severe renal impairment (creatinine clearance less than 10 ml per minute).

Hepatic impairment: The elimination of tramadol may be prolonged. The usual initial dosage should be used but in severe hepatic impairment the dosage interval should be increased to 12 hours.

Administration: Oral; the capsules should be swallowed whole with a drink of water, independent of meals.

4.3 CONTRAINDICATIONS

Tramadol should not be administered to patients who have previously demonstrated hypersensitivity to tramadol or any of the excipients.

In cases of acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs.

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

Tramadol should not be given to patients suffering from uncontrolled epilepsy.

Tramadol should not be given to patients for use in narcotic withdrawal treatment.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Warnings:

At therapeutic doses, tramadol has the potential to cause withdrawal symptoms. Cases of dependence and abuse have been reported rarely.

At therapeutic doses withdrawal symptoms have been reported at a reporting frequency of 1 in 8,000. Reports of abuse and dependence have been less frequent. Because of this potential the clinical need for continued analgesic treatment should be reviewed regularly.

In patients with a tendency to drug abuse or dependence, treatment should be for short periods and under strict medical supervision.

Tramadol is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms.

Tramadol may mask the signs of perforated peptic ulcers.

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 (see section 4.5, *Interaction with other Medicaments and other forms of Interaction).*

Dizziness may increase the risk of falling with associated risk of fracture, particularly in the elderly.

Precautions:

Tramadol should be used with caution in patients with head injury, increased intracranial pressure, severe impairment of hepatic and renal function and in patients prone to convulsive disorders or in shock.

Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered, as the possibility of respiratory depression cannot be excluded in these situations. At therapeutic doses respiratory depression has infrequently been reported.

In one study use of tramadol during general anaesthesia with enflurane and nitrous oxide was reported to enhance intra-operative recall. Until further information is available the use of tramadol during light planes of general anaesthesia should be avoided.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Slow metaboliser status for CYP3A4 and/or CYP2D6 may present a risk for tramadol toxicity (see section 5.2 Pharmacokinetic properties).

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS

Patients treated with monoamine oxidase inhibitors within 14 days prior to administration of the opioid pethidine have experienced life-threatening interactions affecting the central nervous system as well as the respiratory and circulatory centres. The possibility of similar interactions occurring between monoamine oxidase inhibitors and tramadol cannot be ruled out.

Concomitant administration of tramadol with other centrally acting drugs including alcohol may potentiate CNS depressant effects. Combination of mixed agonists/antagonists (e.g. buprenorphine, nalbuphine, pentazocine) and tramadol is not recommended.

Tramadol may increase the potential for both selective serotonin re-uptake inhibitors (SSRIs) tricyclic antidepressants (TCAs), anti-psychotics and other seizure threshold lowering medicinal products to cause convulsions (see section 4.4, *Special Warning and Precautions for Use* and section *5.2, Pharmacokinetic Properties).* In isolated cases there have been reports of serotonin syndrome in a temporal connection with the therapeutic use of tramadol in combination with other serotonergic medicines such as selective serotonin re-uptake inhibitors (SSRIs). Signs of serotonin syndrome may be for example confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea. Withdrawal of the serotonergic medicines usually brings about a rapid improvement. Drug treatment depends on the nature and severity of the symptoms.

Simultaneous administration with cimetidine is associated with clinically insignificant changes in serum concentrations of tramadol. Therefore no alteration of the tramadol dosage regimen is recommended for patients receiving chronic cimetidine therapy.

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. There is a theoretical possibility that tramadol could interact with lithium due to their respective mechanisms of action.

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.

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. The clinical importance of such an interaction has not been studied.

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 have not revealed teratogenic effects although minimal embryotoxicity (delayed ossification) was noted. Fertility, reproductive performance and development of offspring were unaffected. 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. Chronic use during pregnancy may lead to neonatal withdrawal symptoms.

Lactation: 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 should not be administered during breast-feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

Tramadol 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.

4.8 UNDESIRABLE EFFECTS

The most commonly reported adverse reactions are nausea and dizziness, both occurring in 10% of patients.

The frequencies are defined as follows:

Very common: $\geq$ 1/10

Common: $\geq$ 1/100, < 1/10

Uncommon: $\geq$ 1/1000, < 1/100

Rare: $\geq$ 1/10000, < 1/1000

Very rare: < 1/10000

Not known: cannot be estimated from the available data

Blood and lymphatic system disorders

Rare*:* Cases of blood dyscrasias have been rarely observed during treatment with tramadol, but causality has not been established

Immune system disorders

Rare: allergic reactions including dyspnoea, wheezing, bronchospasm and worsening of existing asthma and anaphylaxis have been reported. Urticaria, pruritus and skin rashes have also been reported.

Psychiatric disorders

Rare: confusion, hallucinations, anxiety, changes in appetite dysphoria and nightmares has been reported. 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).

Dependence, abuse and withdrawal reactions have been reported.

Very rare: Typical opiate withdrawal reactions include agitation, anxiety, nervousness, insomnia, hyperkinesias, tremor and gastrointestinal symptoms (see section 4.4, *Special Warning and Precautions for Use and section* and section *4.2, Posology and Method of Administration).*

Very common: dizziness

Common*:* headache, drowsiness

Rare: fatigue, somnolence, respiratory depression, paraesthesia, tremor, involuntary muscle contractions, abnormal coordination, syncope..

Not known: speech disorders epileptiform convulsions have been reported rarely (see section 4.5, *Interactions with other Medicinal products and other forms of Interaction).*Tramadol is known to be associated with the condition serotonin syndrome, particularly at high doses or when given with other drugs that raise serotonin concentrations.

Ear and labyrinth disorders

Very rarely (>0.1%): Tinnitus has been reported.

Eye disorders

Rare: blurred vision

Not known: mydriasis

Cardiac disorders

Uncommon: palpitations, tachycardia, cardiovascular collapse. These adverse reactions may occur especially on intravenous administration and in patients who are physically stressed. Rare: bradycardia

Vascular disorders

Uncommon: orthostatic hypotension and flushing

Rare*:* increase in blood pressure.

Gastrointestinal disorders

Very common: nausea

Common: vomiting, constipation and dry mouth

Uncommon: retching; gastrointestinal irritation (a feeling of pressure in the stomach, bloating), diarrhoea **Hepatobiliary disorders**

In a few isolated cases increases in liver enzyme values have been reported concurrently with the therapeutic use of tramadol.

Skin and subcutaneous tissue disorders Common: diaphoresis (sweating profusely) Rare: angioedema.

Musculoskeletal and connective tissue disorders

Rare: muscle weakness

Renal and urinary disorders

Rare: Difficulty in passing urine, dysuria and urinary retention.

4.9 OVERDOSE:

Symptoms of overdosage are typical of other opioid analgesics, and include miosis, vomiting, cardiovascular collapse, sedation and coma, seizures and respiratory depression. 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 point may be useful in case of intoxication with exceptionally large quantities.

Supportive measures such as maintaining the patency of the airway and maintaining cardiovascular function should be instituted; naloxone should be used to reverse respiratory

depression: fits can be controlled with diazepam. Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore treatment of acute intoxication with tramadol with haemodialysis or haemofiltration alone is not suitable for detoxification.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMICS PROPERTIES

ATC Code: N02AX02

Tramadol is a centrally acting analgesic, effective for moderate to severe acute and chronic pains. Tramadol consists of two enantiomers. The (+)-isomer is predominantly active as an opiate with a higher affinity for the μ-opiate receptor (20 times higher affinity than the (-)isomer). The (+)-desmethyl metabolite will certainly contribute to its action as an opiate as well. The metabolite has a six times stronger affinity for the μ-receptor in vivo than tramadol. In vitro this affinity is 170 times stronger. The (-)-isomer acts as an inhibitor of the re-uptake of noradrenaline and potentiates the analgesic action of the (+)-isomer. The contribution of the stimulation of the serotonin release is considered low. Tramadol has an analgesic and antitussive effect. Unlike morphine respiratory suppression is hardly observed at therapeutic doses. The influence on gastro-intestinal motility and on the cardiovascular system is low at these doses.

5.2 PHARMACOKINETIC PROPERTIES

Tramadol is absorbed rapidly and completely after oral administration. The absolute biological availability is 60-95%, (on average 72%). Maximum serum concentrations are reached after approximately 1 hour. Plasma protein binding amounts to 20%. Tramadol passes the bloodbrain barrier and the placenta.

The excretion of tramadol or its metabolites in human breast milk is small (0.1%).

Tramadol is especially metabolised by demethylation followed by glucuronidisation of the odesmethyl-metabolite. Only o-desmethyl-tramadol is pharmacologically active. Tramadol and its metabolites are almost completely excreted renally, of which approximately 10% as unchanged drug. The half life of the terminal elimination phase of both tramadol and its metabolites is approximately 6 hours, both in young volunteers and in elderly patients. Since tramadol is eliminated both metabolically and renally, the half life of the terminal elimination phase may be prolonged in impaired hepatic and renal function. In those cases the half life of

the terminal elimination phase is twice as long. In patients with both renal and hepatic impairment, the use of tramadol should be avoided.

The inhibition of one or both cytochrome P450 isoenzymes, CYP3A4 and CYP2D6 involved in the metabolism of tramadol, may affect the plasma concentration of tramadol or its active metabolite. This may be a risk for tramadol toxicity.

5.3 PRECLINICAL SAFETY DATA

None stated

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Filleraa-C, Maize Starch BP,

Purified Talc BP

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

24 Months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30^0C, protectec from light and moisture

6.5 NATURE AND CONTENTS OF CONTAINER

Blister Pack of 10 x 10 capsules

6.6 SPECIAL PRECAUTION FOR DISPOSAL

None

MODULE 1: ADMINISTRATIVE INFORMATION AND PRODUCT INFORMATION

7. MARKETING AUTHORIZATION HOLDER

Name	:	**UNOSOURCE PHARMA LTD**
Address	:	Unit : 503-504, 5th floor Hubtown Solaris N.S. Phadke Marg, Andheri (East) Mumbai – 400 069
Phone	:	+91-22-61056105 +91-22-61056106
Fax	:	info@unosourcepharma.com
E-mail	:	

8. MARKETING AUTHORIZATION NUMBERS

Not Applicable

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Not applicable.

10. DATE OF REVISION OF THE TEXT

Not applicable

11. NAME AND ADDRESS OF THE MANUFACTURER

Name	**:** AKUMS DRUGS & PHARMACEUTICALS LTD.
Address	**:** Plant I, Plot No. 19, 20, 21, Sector 6-A, IIE, Sidcul, Ranipur, District: Haridwar, Uttarakhand.
Phone	**:** 91-0133-4325982
Fax	**:** 91-0133-4239219
E-mail	**:** works@akums.in

AKUMS DRUGS & PHARMACEUTICALS LIMITED	Akums
TRADMIN (Tramadol Capsules BP 50 mg)	
MODULE 1: ADMINISTRATIVE INFORMATION AND PRODUCT INFORMATION	

1.4 Product Information

1.4.2 Container labelling:

Pack size: Blister Pack of 10 x 10 Capsules