MCCOY PHARMA PVT LTD

BRAND NAME:	**U-TAMAL CAPSULE**
GENERIC NAME:	**TRAMADOL CAPSULES BP 100mg**

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

1.1 Product Name

Generic Name : TRAMADOL HYDROCHLORIDE CAPSULES B.P. 100 MG

Brand Name : -U-TAMAL CAPSULE

2. Qualitative and quantitative composition

2.1 Label Claim

Each hard gelatin capsule contains:

Tramadol hydrochloride BP 100 mg

Excipients q. s.

Approved colors used in capsule shell

2.2 Quantitative Composition

Batch Size: 100000 Capsules

Sr. No.	Ingredients	Claim	Spec.	Qty/Cap (mg)	(%) Overages	Qty./100000 Capsules (Kg)
Active Ingredient						
1.	Tramadol Hydrochloride	100mg	BP	100.00	NIL	10.000
Excipients						
2.	Maize Starch	-	IP	6.00	NIL	0.600
3.	Maize Starch (additional)	-	IP	0.50	NIL	0.050
4.	Purified Talc	-	IP	2.00	NIL	0.200
5.	Magnesium Stearate	-	IP	1.50	NIL	0.150
6.	Capsule Metallic dark green/metallic yellow size ‘4’	-	IP	01	2	102000
Average Net content per Capsule = 110 mg						

3. Pharmaceu tical form

Hard Gelatin

Capsule

Description: Hard Gelatin Capsule of size "4" with metallic dark green coloured cap and yellow coloured body containing white fine powder.

4.0 Clinical particulars

4.1 Therapeutic indications

The treatment of moderate to severe pain.

4.2 Posology and method of administration

Posology

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.

Adults and children over 12 years

***Acute pain*:** Adults and children over age 12 years: 50-100mg 3-4 times daily. Patients with low weight should use 0.7mg/kg bodyweight. Duration of therapy depends upon clinical need.

***Chronic pain*:** An initial dose of 50mg or 100mg is followed by doses of 50mg or 100mg, every 4 to 6 hours, according to pain severity. The need for continued treatment should be assessed at regular intervals (as withdrawal symptoms and dependence have been reported).

A total daily dose of 400mg should not be exceeded.

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.

Older people

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

Patients with renal impairment/renal dialysis

The elimination of tramadol may be prolonged in these patients. The usual initial dosage should be used. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements.

For patients with creatinine clearance <30ml/min, the dosage interval should be increased to 12 hours. Tramadol is not recommended in patients with severe renal impairment (creatinine clearance <10ml/min). Tramadol is removed very slowly by haemodialysis or haemofiltration so post-dialysis administration to maintain analgesia is not usually necessary.

Patients with hepatic impairment

The elimination of tramadol may be prolonged. The usual dosage should be divided in 2, or the dosage interval should be extended to 12 hours. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements. In severe hepatic impairment, the product is contraindicated.

Paediatric population

Children under 12 years: Not recommended.

Method of administration

The capsules are taken orally, independent of meals, swallowed whole with water

4.3 Contraindications

This product is contraindicated in the following situations:

• Hypersensitivity to the active substance or any of the other.

• Acute intoxication with central nervous system depressants (alcohol, hypnotics, centrally acting analgesics, opioids, psychotropic drugs).

• Patients receiving monoamine oxidase inhibitors or within two weeks of their withdrawal.

• Severe hepatic impairment.

• Severely impaired kidney function (creatinine clearance less than 10ml/min).

• Severe respiratory impairment.

• Epilepsy not controlled by adequate treatment.

• Tramadol must not be administered during breastfeeding if long term treatment, i.e more than 2 to 3 days, is necessary.

• For use in narcotic withdrawal treatment.

4.4 Special warnings and precautions for use

Care should be taken and the risk/benefit of treatment determined prior to administration of tramadol in the following situations:

• Withdrawal symptoms. At therapeutic doses tramadol has the potential to cause withdrawal symptoms. A reporting frequency of 1 in 8000 has been stated. When a patient no longer requires therapy with tramadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

• Drug dependence and abuse. Reports of these are rare and less frequent than withdrawal reactions. The clinical need for analgesic treatment should be reviewed regularly.

Tolerance, psychic and physical dependence may develop, especially after long-term use. In patients with a tendency to drug abuse or dependence. Treatment should only be for short periods and under medical supervision.

• Opioid-dependent patients. Tramadol is not suitable as a substitute in these patients and cannot suppress morphine withdrawal symptoms.

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

• Tramadol should be used with caution in patients with head injury, increased intracranial pressure, impairment of hepatic (metabolism of tramadol and active metabolite is reduced) and renal (decreased rate and extent of excretion of tramadol and the active metabolite) function, decreased level of consciousness and in patients prone to convulsive disorder or in shock.

• Patients prone to convulsive disorders. 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 clinical reasons. The risk of convulsions may increase in patients taking tramadol and concomitant medication that lowers the seizure threshold (see Interactions with other medicaments and other forms of interactions section).

• 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.

• The concomitant use of carbamazepine or concomitant intake of alcohol with tramadol is not recommended.

• Buprenorphine and other mixed agonists-antagonists, naltrexone:

• As there have been fatal cases of unintended overdose with tramadol associated with the use of psych-active medicines or substances including alcohol tramadol should be prescribed with care in alcoholics and users of other psycho-active drugs.

• Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs: Concomitant use of Tramadol and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Tramadol concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms. After long term treatment (> 3 months) of analgesics with use every second day or more frequently, headache may develop or aggravate. Headache caused by overuse of analgesics (MOH - medication-overuse headache) should not be treated by increasing the dose. In such cases the use of analgesics should be discontinued in consultation with a doctor.

CYP2D6 metabolism

Tramadol is metabolized 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 metabolizer there is a risk of developing <side effects> of opioid toxicity even at commonly prescribed doses.

4.5 Interaction with other medicinal products and other forms of

interaction Tramadol 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.

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

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

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.

Tramadol can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors, (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic anti-depressants, anti-psychotics 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. Signs of serotonin syndrome may be for example confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea.

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 oC and inducible or ocular clonus.

Withdrawal of the serotoninergic medicinal products usually brings about a rapid improvement. Treatment depends on the nature and severity of the symptoms.

Sedative medicines such as benzodiazepines or related drugs:

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited.

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 Odemethylated 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 with tramadol revealed at very high doses 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 should not be used in pregnant women.

Tramadol - administered before or during birth - does not affect uterine contractility. In new-born infants it may induce changes in the respiratory rate which are usually not clinically relevant. Chronic use during pregnancy may lead to neonatal withdrawal symptoms.

Breast-feeding

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 400 mg, 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.

Fertility

Post marketing surveillance does not suggest an effect of tramadol on fertility. Animal studies did not show an effect of tramadol on fertility.

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 medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a 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 most commonly reported adverse reactions are nausea and dizziness, both occurring in more than 10 % of patients.

The frequencies are defined as follows:
Very common: ≥1/10
Common: ≥1/100, <1/10
Uncommon: ≥1/1000, <1/100
Rare: ≥1/10 000, <1/1000

Very rare: <1/10 000

Not known: cannot be estimated from the available data

Cardiac disorders:

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

Metabolism and nutrition disorders:

Rare: changes in appetite

Not known: hypoglycaemia

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.

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 which can lower the seizure threshold.

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 as follows: 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

Gastrointestinal disorders:

Very common: nausea

Common: vomiting, constipation, dry mouth

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

Skin and subcutaneous tissue disorders:

Common: hyperhidrosis

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

Musculoskeletal and connective tissue disorders:

Rare: motorial weakness

Hepatobiliary 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.

Renal and urinary disorders:

Rare: micturition disorders (dysuria and urinary retention)

Immune system disorders:
Rare: allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneuroticoedema) and anaphylaxis
General disorders:
Common: fatigue

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, and 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 had 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 or prolonged-release formulation.

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other opioids ATC code: N02A X02

Tramadol is a centrally acting synthetic analgesic compound. 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 (norepinephrine) and enhancement of serotonin release. Tramadol opioid activity derives from low affinity binding of the parent compound to mu-opioid receptors and higher affinity binding of the active metabolite, O-desmethyl tramadol. Compared to morphine, tramadol does not show respiratory depression when given within the analgesic dosage interval. The effect of tramadol is considered 1/10 to 1/6 the effect of morphine. The gastrointestinal motility is not affected. There is minimal effect on the cardiovascular system. The contribution to human analgesia of tramadol relative to the active metabolite is unknown. Tramadol has an antitussive effect. Animal studies have revealed a reduced dependence potential compared with morphine and a very slight tolerance potential.

Paediatric population

Effects of enteral and parenteral administration of tramadol have been investigated in clinical trials involving more than 2000 paediatric patients ranging in age from neonate to 17 years of age. The indications for pain treatment studied in those trials included pain after surgery

(mainly abdominal), after surgical tooth extractions, due to fractures, burns and traumas as well as other painful conditions likely to require analgesic treatment for at least 7 days.

At single doses of up to 2 mg/kg or multiple doses of up to 8 mg/kg per day (to a maximum of 400 mg per day) efficacy of tramadol was found to be superior to placebo, and superior or equal to paracetamol, nalbuphine, pethidine or low dose morphine. The conducted trials confirmed the efficacy of tramadol. The safety profile of tramadol was similar in adult and paediatric patients older than 1 year.

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-metabolized 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,ß = 203 + 40 l). It has a plasma protein binding of about 20 %.

Following a single oral dose administration of tramadol 100 mg as capsules or tablets to young healthy volunteers, plasma concentrations were detectable within approximately 15 to 45 minutes within a mean Cmax of 280 to 208 mcg/L and Tmax of 1.6 to 2h.

Tramadol passes the blood-brain and placental barriers. Very small amounts of the substance and its O-desmethyl derivative are found in the breast-milk (0.1 % and 0.02 % respectively of the applied dose).

Elimination

Elimination half-life t1/2,ß is approximately 6 h, irrespective of the mode of administration.

In patients above 75 years of age it may be prolonged by a factor of approximately 1.4.

In humans tramadol is mainly metabolised by means of N- and O-demethylation and conjugation of the O-demethylation products with glucuronic acid. Only O-desmethyltramadol is pharmacologically active. There are considerable interindividual quantitative differences between the other metabolites. So far, eleven metabolites have been found in the urine. Animal experiments have shown that O-desmethyltramadol is more potent than the parent substance by the factor 2 - 4. Its half-life t1/2,ß (6 healthy volunteers) is 7.9 h (range 5.4 - 9.6 h) and is approximately that of tramadol.

Biotransformation

The inhibition of one or both types of the isoenzymes CYP3A4 and CYP2D6 involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolite.

Tramadol and its metabolites are almost completely excreted via the kidneys. Cumulative urinary excretion is 90 % of the total radioactivity of the administered dose. In cases of impaired hepatic and renal function the half-life may be slightly prolonged. In patients with

cirrhosis of the liver, elimination half-lives of 13.3 + 4.9 h (tramadol) and 18.5 + 9.4 h (O-desmethyltramadol), in an extreme case 22.3 h and 36 h respectively, have been determined. patients with renal insufficiency (creatinine clearance < 5 ml/min) the values were 11 + 3.2 h and 16.9 + 3 h, in an extreme case 19.5 h and 43.2 h respectively.

Linerarity/non-linerity

Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range.

The relationship between serum concentrations and the analgesic effect is dose-dependent, but varies considerably in isolated cases. A serum concentration of 100 - 300 ng/ml is usually effective.

Paediatric population

The pharmacokinetics of tramadol and O-desmethyltramadol after single-dose and multiple-dose oral administration to subjects aged 1 year to 16 years were found to be generally similar to those in adults when adjusting for dose by body weight, but with a higher between-subject variability in children aged 8 years and below.

In children below 1 year of age, the pharmacokinetics of tramadol and Odesmethyltramadol have been investigated, but have not been fully characterized. Information from studies including this age group indicates that the formation rate of O-desmethyltramadol via CYP2D6 increases continuously in neonates, and adult levels of CYP2D6 activity are assumed to be reached at about 1 year of age. In addition, immature glucuronidation systems and immature renal function may result in slow elimination and accumulation of O-desmethyltramadol in children under 1 year of age.

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 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 tumors. In the study in mice there was an increased incidence of liver cell adenomas in male animals (a dose-dependent, non-significant increase from 15 mg/kg upwards) and an increase in pulmonary tumours in females of all dosage groups (significant, but not dose-dependent).

6. Pharmaceutical particulars

6.1 List of excipients

Maize Starch
Purified Talc
Magnesium Stearate
Capsule Metallic dark green/metallic Yellow size '4'

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 30°C.
Keep out of reach of children
Discard outdated medicines.

6.5 Nature and contents of container

10 Capsules are packed in Alu-PVC Blister, Such 10 blisters Packed in a Carton along with Patient Information Leaflet.

6.6 Special precautions for disposal and other handling

None stated.

7. Manufactured by

MCCOY PHARMA PVT.LTD.,
Plot S-12, M.I.D.C. Tarapur,
Boisar, Dist - Thane 401 506, Maharashtra, India.

8. MARKETING AUTHORISATION HOLDER:

LONGRICH PHARMACEUTICAL LIMITED

1, EMENIKE CLOSE, IKOSI KETU, LAGOS

STATE