1.3.1 SUMMARY OF PRODUCT CHARACTERISTIC:

1. NAME OF THE MEDICINAL PRODUCT: Tramadol

Capsules BP

2. Qualitative and Quantitative Composition

Composition:

Each Hard Gelatin Capsule Contains:

Tramadol Hydrochloride BP…….. 100 mg

Excipients……Q.S.

Approved Colours used in Capsules shells

For the full list of excipients, see section 6.1

3. Pharmaceutical Form

Solid Dosage form (Hard Gelatin, Capsules)

Green/yellow coloured unsealed Hard gelatin capsules, size "4" containing almost white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment and prevention of moderate to severe pain.

4.2 Posology and method of administration

Posology

The dose of Tramadol Capsules BP 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.

Dosage for adults and adolescents aged 12 years and older is:

For acute pain - an initial dose of 100 mg is usually necessary. This can be followed by doses of 50 mg or 100 mg not more frequently than 4 hourly, and duration of therapy should be matched to clinical need.

For pain associated with chronic conditions -use in an initial dose of 50 mg and then titrate dose according to pain severity. The need for continued treatment should be assessed at regular intervals as withdrawal symptoms and dependence have been reported, although rarely.

Paediatric population:

Tramadol Capsules BP should not be taken by children under 12 years of age, since safety and efficacy have not been established.

Elderly patients:

A dose adjustment is usually necessary in patients up to 75 years of age without clinically manifest hepatic or renal insufficiency. In elderly patients over 75 years of age elimination may be prolonged. Therefore, if necessary the dosage interval is to be extended according to the patient's requirements.

Patients with renal or hepatic impairment:

In patients with renal and/or hepatic insufficiency the elimination of Tramadol Capsules BP is delayed. In these patients prolongation of the dosage intervals 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 Capsules BP is not recommended.

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

Method of administration

The capsules are to be taken whole with sufficient liquid, independently of meals.

Swallow the capsules whole with some water without chewing.

If you have difficulty in swallowing, you may open the capsules. You must open them very carefully by pulling and twisting each end over a spoon so that all the pellets stay in the spoon. Do not chew. Swallow all the pellets with water.

4.3 Contraindications

Tramadol Hydrochloride is contraindicated in the following patients:

- Hypersensitivity to the active substance tramadol hydrochloride or to any of the excipients.
- 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 inhibitors or within 2 weeks of their withdrawal.
- Uncontrolled epilepsy.

Tramadol must not be used for narcotic withdrawal treatment.

4.4 Special warnings and special precautions for use

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:

Concomitant use of Tramadol Capsules BP 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 Capsules BP 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

<u>Sleep-related breathing disorders:</u>

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

<u>Risk of tolerance, dependence and withdrawal symptoms:</u>

Tolerance, psychic and physical dependence may develop, especially after long-term use. 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 reporting frequency of 1 in 8,000. Reports of dependence and abuse have been less frequent. Because of this potential the clinical need for continued analgesic treatment should be reviewed regularly.

When a patient no longer requires therapy with tramadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

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

Tramadol Capsules BP are not a suitable substitute in opioid dependent patients. The product does not suppress morphine withdrawal symptoms although it is an opioid agonist.

CYP2D6 metabolism:

Tramadol is metabolised 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 metaboliser there is a risk of developing side effects of opioid toxicity even at commonly prescribed doses.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised below:

Population	**Prevalence %**
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1% to 2%

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

Adrenal insufficiency:

Opioid analgesics may occasionally cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of acute or chronic adrenal insufficiency may include e.g. severe abdominal pain, nausea and vomiting, low blood pressure, extreme fatigue, decreased appetite, and weight loss.

Paediatric population:

Post-operative use in children:

There have been reports in the published literature that tramadol given postoperatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events. Extreme caution should be exercised when tramadol is administered to children for post-operative pain relief and should be accompanied by close monitoring for symptoms of opioid toxicity including respiratory depression.

Children with compromised respiratory function:

Tramadol is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures.

In patients with severe renal or hepatic impairment, head injury, increased intracranial pressure, or patients in shock or at risk of convulsions, Tramadol Capsules BP should be used with caution.

At present Tramadol Capsules BP 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 Tramadol Capsules BP to patients with existing respiratory depression or to patients taking concomitant CNS depressant drugs.

4.5 Interaction with other medicinal products and other forms of Interaction

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.

Tramadol Capsules BP may potentiate the CNS depressant effects of other centrally acting drugs (including alcohol) when administered concomitantly with such 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.

Tramadol can induce convulsions and increase the potential for selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, 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. 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.

Administration of Tramadol Capsules BP together with carbamazepine results in markedly decreased serum concentrations of tramadol which may reduce analgesic effectiveness and shorten the duration of action.

Theoretically, tramadol could interact with noradrenaline, 5-HT or lithium, due to their mechanisms of action, and thus potentiate their anti-depressant effect. However there have been no reports of such interactions.

Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (e.g. warfarin) due to reports of increased INR and ecchymoses in some patients.

4.6 Fertility, pregnancy and lactation

Pregnancy

Tramadol Capsules BP should not be used in pregnancy, as there is inadequate evidence available to assess the safety of tramadol in pregnant women. Studies of tramadol in rats and rabbits have revealed no teratogenic effects. However, embryotoxicity was shown in the form of delayed ossification. Fertility, reproductive performance and development of offspring were unaffected.

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 breastfed 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.

4.7 Effects on ability to drive and use machines

Tramadol Capsules BP may cause drowsiness and this effect may be potentiated by alcohol and other CNS depressants. Patients should be warned not to drive or operate machinery.

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

Gastrointestinal system:

Frequently (>10%):- nausea

occasionally (1-10%): vomiting, dry mouth and constipation.

Central nervous system and psychiatric:

Frequently (>10%): dizziness

occasionally (1-10%): headache and drowsiness

In very rare cases (<0.1%) somnolence, fatigue, blurred vision, confusion, hallucinations, respiratory depression, dysphoria, nightmares and parasthesia have been reported. Very rarely epileptiform convulsions have been reported occurring mainly after administration of high doses of tramadol or after treatment with drugs which can lower the seizure threshold or themselves induce cerebral convulsions (e.g. anti-depressants or anti-psychotics).

Dependence/Withdrawal reactions: Prolonged administration of tramadol may lead to dependence. In very rare cases (<0.1%) typical opiate withdrawal reactions including agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms have been reported

Allergic/anaphylactoid reactions:

In very rare cases (<0.1%) allergic reactions (dyspnoea, wheezing, bronchospasm and worsening of asthma) and anaphylaxis have been reported. Pruritus, urticaria and skin rashes have also been reported.

Cardiovascular System:

Rarely (<1%): palpitations, tachycardia, orthostatic hypotension, flushing

very rarely (<0.1%): bradycardia, hypertension, syncope.

Respiratory, thoracic and mediastinal disorders:

Frequency unknown: Hiccups

Metabolism and nutrition disorders:

Frequency not known (cannot be estimated from the available data): hypoglycaemia.

Other adverse events:

Occasionally (1-10%): sweating

very rarely (<0.1%): micturition disorders. There have also been cases of blood dyscrasias observed with tramadol treatment, but direct causality has not been confirmed. In a few isolated cases increases in liver enzyme values have been reported concurrently with the therapeutic use of tramadol.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

Symptoms of tramadol overdose include vomiting, miosis, sedation, coma, seizures, cardiovascular collapse and respiratory depression. Such symptoms are typical of opioid analgesics.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesic

ATC code: N02AX02

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 duration of analgesia with orally administered tramadol has been shown to be 3-6 hours with maximum pain relief at 1-4 hours post-dosing. Tramadol also has an antitussive action but has no effect on gastrointestinal motility. At the recommended dosages, the effects of tramadol given orally on the respiratory and cardiovascular systems appear to be clinically insignificant.

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 2mg/kg or multiple doses of up to 8mg/kg per day (to a maximum of 400mg 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 that 1 year

5.2 Pharmacokinetic properties

a) General:

Following oral dosing, tramadol is rapidly and almost completely absorbed. After oral administration as capsules or tablets, tramadol appears in the plasma within 15 - 45 minutes, reaching peak plasma concentrations at a mean of 2 hours. The mean oral bioavailability of tramadol is approximately 68% after single doses and increases to 90 to 100% on multiple administrations.

The half-life absorption for oral tramadol (solid dose formulation) is 0.38 ± 0.18 hours with a peak plasma concentration of 280 ± 49 ng/ml 2 hours after oral dosing with 100 mg tramadol (solid dose formulation). Tramadol has a high tissue affinity with an apparent volume of distribution of 306 litres after oral dosing in healthy volunteers.

Tramadol undergoes hepatic metabolism with approximately 85% of an oral 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. The mean elimination half-life of tramadol following oral administration is 5 - 6 hours. Approximately 90% of an oral dose is excreted by the kidneys.

The inhibition of one or both cytochrome P450 isoenzymes, CYP3A4 and CYP2D6 involved in the biotransformation of tramadol, may affect the plasma concentration of tramadol or its active metabolite.

b) 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.

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 O-desmethyltramadol 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.

Effect of hepatic or renal impairment: As both tramadol and its pharmacologically active metabolite, O-demethyl 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.

5.3 Preclinical safety data

The standard range of pharmacodynamic, pharmacokinetic 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.

6. Pharmaceutical particulars

6.1 List of excipients

Maize Starch

Maize Starch (for Paste)

Calcium Carbonate

Sodium Methyl Hydroxybenzoate

Sodium Propyl Hydroxybenzoate

Povidone

Purified Water

Purified Talc

Magnesium Stearate

Empty Hard Gelatin Capsules Yellow Colour Size - “4”

6.2 Incompatibilities

No pharmaceutical incompatibilities reported

6.3 Shelf life

36 months

6.4 Special precautions for storage

No special requirements.

6.5 Nature and contents of container

Alu- PVC blister of 10 capsules, such 10 blisters are packed in a primary carton along with pack insert.

6.6 Instructions for use and handling

Not available

7. Manufacturer

McW Healthcare Pvt. Ltd.

286, 287 A, 287 B,

Sector-E, Industrial Area,

Sanwer Road, Indore (M.P).

8. Marketing Authorization Holder

XXXX

9. Marketing Authorization Number (S)

XXXX

10. Date of First Authorization/Renewal of the Authorisation

XXXX

11. Date of Revision of the Text

XXXX