1. NAME OF THE MEDICINAL PRODUCT

Brand Name : METRAK Tramadol 100

Generic Name : Tramadol Capsules BP 100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Hard Gelatin Capsule Contains:

Tramadol Hydrochloride BP…..100 mg

Excipients ..... q.s.

Colour: Approved colour used in empty capsule shell.

3. PHARMACEUTICAL FORM: Oral Capsules.

4. Clinical particulars

4.1 Therapeutic indications:

METRACK Tramadol Capsules are indicated for the management (treatment and prevention) ofmoderate to severe pain.

Posology and method of administration:

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

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.

Elderly patients

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.

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.

Dosage in Children

Children under 12 years: Not recommended.

Method of administration

For oral use.

4.2 Contraindications

This product is contraindicated in the following situations:

• Previously demonstrated hypersensitivity to tramadol or any of the other ingredients in the capsule.

• 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.

4.3 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.

• 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.

• 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 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.

• 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.

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.

4.4 Interaction with other medicinal products and other forms of interaction

Tramadol should not be combined with MAO inhibitor.

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 (see section 4.3), 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 °C 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.

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.

4.5 Pregnancy and Lactation

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. During lactation about 0.1 % of the maternal dose is secreted into the milk. Tramadol is not recommended during breast-feeding. After a single administration of tramadol it is not usually necessary to interrupt breast-feeding.

4.6 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.

4.7 Undesirable effects

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

Cardiovascular disorders:

Uncommon (1/1000, <1/100): cardiovascular regulation (palpitation, tachycardia, postural hypotension or cardiovascular collapse). These adverse reactions may occur especially on intravenous administration and in patients who are physically stressed.

Rare (1/10000, <1/1000): bradycardia, increase in blood pressure

Nervous system disorders:

Very common (1/10): dizziness

Common (1/100, <1/10): headache, somnolence

Rare (1/10000, <1/1000): changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope.

If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly respiratory depression may occur.

Epileptiform convulsions occurred mainly after administration of high doses of tramadol or after concomitant treatment with medicinal products which can lower the seizure threshold.

Not known: speech disorders

Psychiatric disorders:

Rare (1/10000, <1/1000): hallucinations, confusion, sleep disturbance, 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).

Dependence may occur.

Eye disorders:

Rare (1/10000, <1/1000): blurred vision

Respiratory disorders:
Rare (1/10000, <1/1000): dyspnoea

Worsening of asthma has been reported, though a causal relationship has not been established.

Gastrointestinal disorders:

Very common (1/10): nausea
Common (1/100, <1/10): vomiting, constipation, dry mouth
Uncommon (1/1000, <1/100): retching; gastrointestinal irritation (a feeling of pressure in the stomach, bloating), diarrhea

Skin and subcutaneous disorders:

Common (1/100, <1/10): sweating
Uncommon (1/1000, <1/100):dermal reactions (e.g. pruritus, rash, urticaria)

Musculoskeletal disorders:

Rare (1/10000, <1/1000): 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 (1/10000, <1/1000): micturition disorders (difficulty in passing urine, dysuria and urinary retention)

General disorders:

Common (1/100, <1/10): fatigue

Rare (1/10000, <1/1000): allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis; Symptoms of withdrawal reactions, 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.

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.

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 Pharmacodynamic 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 anti-tussive 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.

Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin *in vitro*, as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile. Analgesia in humans begins approximately within one hour after administration and reaches a peak in approximately two to three hours.

Apart from analgesia, Tramadol administration may produce a constellation of symptoms (including dizziness, somnolence, nausea, constipation, sweating and pruritus) similar to that of other opioids. In contrast to morphine, tramadol has not been shown to cause histamine release. At therapeutic doses, Tramadol has no effect on heart rate, left-ventricular function or cardiac index. Orthostatic hypotension has been observed.

5.2 Pharmacokinetic properties

The analgesic activity of tramadol is due to both parent drug and the M1 metabolite. Tramadol is administered as a racemate and both the [-] and [+] forms of both tramadol and M1 are detected in the circulation. Tramadol is well absorbed orally with an absolute bioavailability of 75%. Tramadol has a volume of distribution of approximately 2.7L/kg and is only 20% bound to plasma proteins. Tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites. One metabolite, M1, is pharmacologically active in animal models. The formation of M1 is dependent upon CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response.. Tramadol and its metabolites are excreted primarily in the urine with observed plasma half-lives of 6.3 and 7.4 hours for tramadol and M1, respectively. Linear pharmacokinetics have been observed following multiple doses of 50 and 100 mg to steady-state.

Absorption

Racemic tramadol is rapidly and almost completely absorbed after oral administration. The mean absolute bioavailability of a 100 mg oral dose is approximately 75%. The mean peak plasma

concentration of racemic tramadol and M1 occurs at two and three hours, respectively, after administration in healthy adults. In general, both enantiomers of tramadol and M1 follow a parallel time course in the body following single and multiple doses although small differences (~ 10%) exist in the absolute amount of each enantiomer present.

Steady-state plasma concentrations of both tramadol and M1 are achieved within two days with q.i.d. dosing. There is no evidence of self-induction.

Figure 1: Mean Tramadol and M1 Plasma Concentration Profiles after a Single 100 mg Oral Dose and after Twenty-Nine 100 mg Oral Doses of Tramadol HCl given q.i.d.

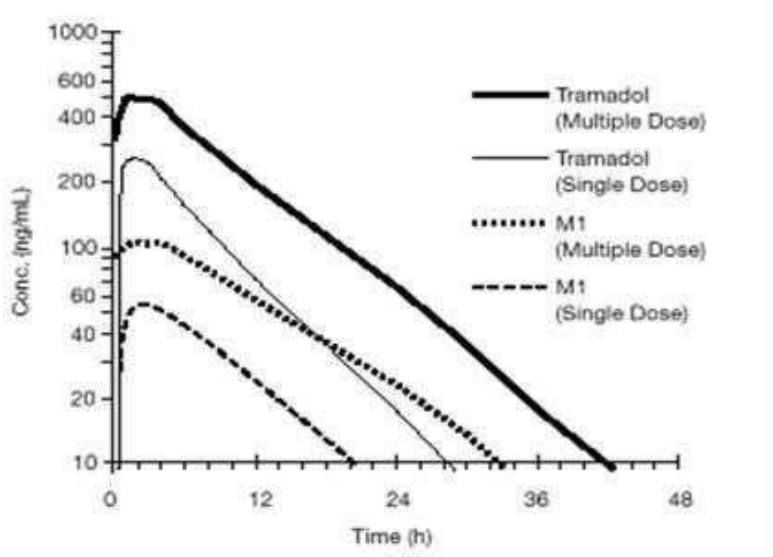

Table 1 Mean (%CV) Pharmacokinetic Parameters for Racemic Tramadol and M1 Metabolite

Population/Dosage RegimenSD = Single dose, MD = Multiple dose, p.o.= Oral administration, i.v.= Intravenous administration, q.i.d. = Four times daily	**Parent Drug/ Metabolite**	**PeakConc. (ng/mL)**	**Time to Peak (hrs)**	**Clearance/FF represents the oral bioavailability of tramadol (mL/min/Kg)**	**$t_{1/2}$ (hrs)**

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Healthy Adults, 100 mg qid, MD p.o	Tramadol M1	592 (30) 110 (29)	2.3 (61) 2.4 (46)	5.90 (25) [1]	6.7 (15) 7.0 (14)
Healthy Adults, 100 mg SD p.o	Tramadol M1	308 (25) 55.0 (36)	1.6 (63) 3.0 (51)	8.50 (31)	5.6 (20) 6.7 (16)
Geriatric, (<75 yr) 50 mg SD p.o.	Tramadol M1	208 (31) [2]	2.1 (19)	6.89 (25)	7.0 (23)
Hepatic Impaired, 50 mg SD p.o.	Tramadol M1	217 (11) 19.4 (12)	1.9 (16) 9.8 (20)	4.23 (56)	13.3 (11) 18.5 (15)
Renal Impaired, CLcr10-3mL/min	Tramadol M1			4.23 (54)	10.6 (31)

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Population/Dosage RegimenSD = Single dose, MD = Multiple dose, p.o.= Oral administration, i.v.= Intravenous administration, q.i.d. = Four times daily	**Parent Drug/ Metabolite**	**PeakConc. (ng/mL)**	**Time to Peak (hrs)**	**Clearance/FF represents the oral bioavailability of tramadol (mL/min/Kg)**	**$t_{1/2}$ (hrs)**
100 mg SD i.v.					11.5 (40)
Renal Impaired, CL_{cr}<5 mL/min 100 mg SD i.v.	Tramadol M1			3.73 (17)	11.0 (29) 16.9 (18)

[1] Not applicable

[2] Not measured

Food Effects

Oral administration of tramadol is with food does not significantly affect its rate or extent of absorption, therefore, tramadol is can be administered without regard to food.

Distribution

The volume of distribution of tramadol was 2.6 and 2.9 liters/kg in male and female subjects, respectively, following a 100 mg intravenous dose. The binding of tramadol to human plasma proteins is approximately 20% and binding also appears to be independent of concentration up to 10µg/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically

relevant range.

Metabolism

Tramadol is extensively metabolized after oral administration. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The remainder is excreted either as unidentified or as unextractable metabolites. 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. Formation of M1 is dependent on CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response.

Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P-450. These individuals are "poor metabolizers" of debrisoquine, dextromethorphan, tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase I studies in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers", while M1 concentrations were 40% lower. Concomitant therapy with inhibitors of CYP2D6 such as fluoxetine, paroxetine and quinidine could result in significant drug interactions. *In vitro* drug interaction studies in human liver microsomes indicate that inhibitors of CYP2D6 such as fluoxetine and its metabolite norfluoxetine, amitriptyline and quinidine inhibit the metabolism of tramadol to various degrees, suggesting that concomitant administration of these compounds could result in increases in tramadol concentrations and decreased concentrations of M1. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown. Concomitant use of SEROTONIN re-uptake INHIBITORS and MAO INHIBITORS may enhance the risk of adverse events, including seizure and serotonin syndrome.

Elimination

Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. The mean terminal plasma elimination half-lives of racemic tramadol and racemic M1 are 6.3 ± 1.4 and 7.4 ± 1.4 hours, respectively. The plasma elimination half-life of racemic tramadol increased from approximately six hours to seven hours upon multiple dosing.

Special Populations

Renal

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. In patients with creatinine clearances of less than 30 mL/min, adjustment of the dosing regimen is recommended. The total amount of tramadol and M1 removed during a 4-hour dialysis period is less than 7% of the administered dose.

Hepatic

Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver, resulting in both a larger area under the concentration time curve for tramadol and longer tramadol and M1 elimination half-lives (13 hrs. for tramadol and 19 hrs. for M1). In cirrhotic patients, adjustment of the dosing regimen is recommended .

Geriatric

Healthy elderly subjects aged 65 to 75 years have plasma tramadol concentrations and elimination half-lives comparable to those observed in healthy subjects less than 65 years of age. In subjects over 75 years, maximum serum concentrations are elevated (208 vs. 162 ng/mL) and the elimination half-life is prolonged (7 vs. 6 hours) compared to subjects 65 to 75 years of age. Adjustment of the daily dose is recommended for patients older than 75 years.

Gender

The absolute bioavailability of tramadol was 73% in males and 79% in females. The plasma clearance was 6.4 mL/min/kg in males and 5.7 mL/min/kg in females following a 100 mg IV dose of tramadol. Following a single oral dose, and after adjusting for body weight, females had a 12% higher peak tramadol concentration and a 35% higher area under the concentration-time curve compared to males. The clinical significance of this difference is unknown.

5.3 Preclinical safety data

NA

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnessium stearate BP

Talcum BP

Aerosil BP

Starch BP

Cap Metallic white /Body metallic green coloured Size "2" Hard gelatin capsules, containing white granular powder.

6.1 Incompatibilities

Not Applicable

6.2 Shelf life

36 months from the Date of Manufacture.

6.3 Special precautions for storage

Store below 30°C.

6.4 Nature and contents of container and special equipment for use, administration or implantation:

20 x 10 Capsules pack in an carton along with insert.

6.5 Special precautions for disposal and other handling:

No any precaution

7. APPLICANT/MANUFACTURER:

Merit organics Ltd

Factory Address -: Plot No. 2104/2/A,

GIDC, Sarigam, Bhilad,

Dist.- Valsad - 396155,

Gujarat, INDIA