1.6.1

Prescribing Information

(Summary of Product Characteristics)

1.6.1 Summary of Product Characteristics(SPC)

1. NAME OF THE MEDICINAL PRODUCT

KLAMADOL (Tramadol Hydrochloride Injection 50mg/ml)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Name of the product : KLAMADOL

Generic Name **:** Tramadol Hydrochloride Injection 50mg/ml

Strength **:** Each ml contains:

Tramadol hydrochloride BP…….50 mg

Water for injection BP ……. q.s.

3. PHARMACEUTICAL FORM:

Liquid Injection

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications:

For the treatment and prevention of moderate to severe pain.

4.2 Posology and Method of administration

Method of Administration:

- KLAMADOL should not be administered for longer than absolutely necessary. If long-term pain treatment with KLAMADOL is necessary in view of the nature and severity of the illness, then careful regular monitoring should be carried out (if necessary with breaks in treatment) to establish whether, and to what extent, further treatment is necessary.
- 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 total daily dose of 400mg KLAMADOL hydrochloride should not be exceeded, except in special clinical circumstances.
- The KLAMADOL solution is for parenteral injection either intramuscularly, by slow intravenous injection or diluted in solution for administration by infusion or patient controlled analgesia.

Posology:

Adults and children 12 years and over:

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

For post-operative pain, an initial bolus of 100mg is administered. During the 60 minutes following the initial bolus, further doses of 50mg may be given every 10-20 minutes, up to a total dose of 250mg including the initial bolus. Subsequent doses should be 50mg or 100mg 4- 6 hourly up to a total daily dose of 400mg.

Geriatric 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 insufficiency/dialysis and hepatic impairment:

In patients with renal and/or hepatic insufficiency the elimination of KLAMADOL is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements.

Children under 12 years:

Not recommended.

4.3 Contraindications

KLAMADOL should not be given to patients who have previously demonstrated hypersensitivity towards tramadol or any of the other ingredients. KLAMADOL should not be given to patients suffering from acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs.

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

KLAMADOL is contraindicated in patients with epilepsy not adequately controlled by treatment.

KLAMADOL must not be used in narcotic withdrawal treatment.

4.4 Special warning and Precautions for use.

Warnings

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

At therapeutic doses withdrawal symptoms have been reported at a frequency of 1 in 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.

Tolerance, psychic and physical dependence may develop, especially after long-term use. 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 50mg/ml Solution for Injection is not a suitable substitute in opioid dependent patients. The product does not suppress morphine withdrawal symptoms although it is an opioid agonist.

Tramadol 50mg/ml Solution for Injection may cause drowsiness and this effect may be potentiated by alcohol and other CNS depressants. Ambulant patients should be warned not to drive or operate machinery if affected (see section 4.7 Effects on the ability to drive and use machines)

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%

Post-operative use in children

There have been reports in the published literature that tramadol given post-operatively 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. These factors may worsen symptoms of opioid toxicity.

Precautions

Tramadol 50mg/ml Solution for Injection should be used with caution in opioid-dependent patients, patients with head injury, a reduced level of consciousness of uncertain origin, disorders of the respiratory centre or function, increased intracranial pressure, severe

impairment of hepatic and renal function and in patients prone to convulsive disorders or in shock. In patients sensitive to opiates the product should only be used with caution.

Convulsions have been reported at therapeutic doses and the risk may be increased at doses exceeding the usual upper daily dose limit (400mg). 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 'Interactions with other Medicinal Products and other Forms of Interactions').

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

In one study using a nitrous oxide/opioid (tramadol) anaesthetic technique (with only intermittent administration of enflurane 'as required') tramadol was reported to enhance intra-operative recall. Hence its use during potentially very light planes of general anaesthesia should be avoided.

Two studies of tramadol administration during anaesthesia comprising continuous administration of isoflurane have shown clinically significant lightening of anaesthetic depth or intra-operative recall. Therefore providing the current practice of administering continuous, potent (volatile or intravenous) anaesthetic agent is followed, tramadol may be used intra-operatively in the same way as other analgesic agents are routinely used.

This medicinal product contains approximately 8.29mg sodium acetate trihydrate (1.4mg sodium) per 2ml dose.

4.5 Interactions with other medicinal products and other forms of interaction

KLAMADOL 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 KLAMADOL .

Concomitant administration of KLAMADOL with other centrally acting drugs, including alcohol, may potentiate CNS depressant effects. KLAMADOL can induce convulsions and

increase the potential for selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and other seizure threshold-lowering medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.

Theoretically there is a possibility that KLAMADOL could interact with lithium. There have been no reports of this potential interaction.

Concomitant therapeutic use of KLAMADOL 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.

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

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

Carbamazepine – The simultaneous administration of carbamazepine markedly decreases serum concentrations of KLAMADOL to an extent that a decrease in analgesic effectiveness and a shorter duration of action may occur.

Cimetidine - With the concomitant or previous administration of cimetidine clinically relevant interactions are unlikely to occur. Therefore no alteration of the KLAMADOL dosage regimen is recommended for patients receiving chronic cimetidine therapy.

Quinidine - A study in 12 healthy volunteers has shown that quinidine causes an approximate 25% increase in the KLAMADOL Cmaxand AUC; Tmax is unaffected. However, the increases in Cmax and AUC fall within the normal therapeutic range for KLAMADOL, and no dosage adjustment is required.

Other active substances known to inhibit CYP3A4, such as ketoconazole and erythromycin, might inhibit the metabolism of KLAMADOL (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 KLAMADOL in patients with postoperative pain.

4.6 Pregnancy and Lactation

Pregnancy

Animal studies with KLAMADOL at very high doses have revealed effects on organ development, ossification and neonatal mortality KLAMADOL crosses the placenta. There is inadequate evidence available on the safety of KLAMADOL in human pregnancy, therefore KLAMADOL should not be used in pregnant women.

KLAMADOL - 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.

Breast-feeding

Approximately 0.1% of the maternal dose of KLAMADOL 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 KLAMADOL ingested by breast-fed infants of 3% of the maternal weight- adjusted dosage. .

For this reason KLAMADOL should not be administered during breast-feeding or alternatively, breast-feeding should be discontinued during treatment with KLAMADOL.. After a single administration of KLAMADOL however, it is not usually necessary to interrupt breast feeding.

Fertility

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

4.7 Effects on ability to drive and use machines

KLAMADOL may cause somnolence and dizziness and these effects may be potentiated by alcohol and other CNS depressants. Ambulant patients should be warned not to drive or operate machinery if affected.

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 todrive

• Do not drive until you know how the medicine affectsyou

• 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

Rapid intravenous administration may be associated with a higher incidence of adverse effects and therefore should be avoided. The most commonly reported adverse drug reactions are nausea and dizziness, both occurring in more than 10 % of patients.

The frequencies are defined as follows:

Very 1/10 Common: 1/100, <1/10 1/1000, <1/100 1/10 000, <1/1000

Very rare: <1/10 000

Not known: cannot be estimated from the available data

Cardiovascular system disorders:

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

Rare: bradycardia, increase in blood pressure.

Nervous system disorders:

Very common: dizziness.

Common: headache, somnolence.

Rare: changes in appetite, paraesthesia, tremor, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope, speech disorders.

Epileptiform convulsions occurred mainly after administration of high doses of KLAMADOL 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 side effects may occur following administration of KLAMADOL, which vary individually in intensity and nature (depending on personality and duration of medication). These include changes in mood (usually elation, occasionally dysphoria), changes in activity (usually suppression, occasionally increase) and changes in cognitive and sensorial ability (e.g. decision behaviour, perception disorders). Dependence may occur.

Eye disorders:

Rare; blurred vision, miosis, mydriasis.

Respiratory system 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.

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 disorders:

Common: sweating.

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

Musculo-skeletal system disorders:

Rare: muscle weakness.

Hepatobiliary system disorders:

In a few isolated cases, increases in liver enzyme values have been reported in a temporal connection with the therapeutic use of KLAMADOL.

Renal and urinary system disorders:

Rare: micturition disorders (difficulty in passing urine, dysuria and urinary retention)

General disorders:

Common: fatigue.

Immune system disorders

Rare: allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis.

Metabolism and nutrition disorders:

Not known: hypoglycaemia

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 KLAMADOL discontinuation include: panic attacks, severe anxiety, hallucinations, paraesthesias, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, personalisation, derealisation, paranoia).

4.9 Overdose

Symptoms

In principle, on intoxication with KLAMADOL symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include in particular miosis, vomiting,

cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Treatment

The general emergency measures apply. Keep open the respiratory tract (aspiration!), maintain respiration and circulation depending on the symptoms. The antidote for respiratory depression is naloxone. In animal experiments naloxone 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 KLAMADOL intake. Gastrointestinal decontamination at a later time point may be useful in case of intoxication with exceptionally large quantities.

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

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics

ATC code: N 02A X02

KLAMADOL is a centrally acting analgesic. 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 and enhancement of serotonin release.

KLAMADOL has an antitussive effect. In contrast to morphine, analgesic doses of KLAMADOL over a wide range have no respiratory depressant effect. Also gastrointestinal motility is less affected. Effects on the cardiovascular system tend to be slight. The potency of KLAMADOL is reported to be 1/10 (one tenth) to 1/6 (one sixth) that of morphine.

5.2 Pharmacokinetic properties

More than 90% of tramadol is absorbed after oral administration. The mean absolute bioavailability is approximately 70 %, irrespective of the concomitant intake of food. The

difference between absorbed and non-metabolised available tramadol is probably due to the low first-pass effect. The first-pass effect after oral administration is a maximum of 30 %.

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 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.

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. In 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.

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 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.

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 tumours. 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

Following excipients are used in the formulation of KLAMADOL.

Sodium Acetate (Trihydrate)

Glacial Acetic acid

Water for Injection

6.2 Incompatibilities

Precipitation will occur if Tramadol 50mg/ml Solution for Injection is mixed in the same syringe with injections of diazepam, diclofenac sodium, indometacin, midazolam and piroxicam.

Tramadol 50mg/ml Solution for Injection must not be mixed with other medicinal products except those mentioned above.

6.3 Shelf life

30 months from the date of manufacture.

6.4 Special precautions for storage

Store below 30°C, protected from light. Do not allow to freeze.

6.5 Nature and contents of container

Each 2ml Flint ampoule USP type-I is filled, sealed and labeled. 10 such ampoules are to be placed in a transparent tray & inserted along with leaflet in printed carton.

6.6 Instructions for use and handling

Keep out of reach of children.

7.MARKETING AUTHORISATION HOLDER

Manufactured and Marketed by:

KILITCH DRUGS (INDIA) LTD.

C-301/2 TTC Industrial area MIDC Pawane village Navi Mumbai- 400 705 INDIA

8. MARKETING AUTHORISATION NUMBER(S) :

Not Applicable

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

Not Applicable

10. DATE OF REVISION OF THE TEXT:

Not Applicable

The Summary of Product Characteristics (SPC) is satisfactory.

11. DOSIMETRY (IF APPLICABLE):

Not Applicable

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE):

Not Applicable