1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

1. Name of medicinal product

KUKA TRAMADOL 50 MG

2. Composition:

Each hard gelatin capsule contains:
Tramadol Hydrochloride BP 50mg
Excipients q .s.
Approved colors used in capsules shells

3. Pharmaceutical Form:

A green / yellow gelatin capsule containing Tramadol Capsules BP which is packed in 1 strip of alu pvc blister of 10 capsules in a carton along with insert.

4. Clinical Particulars

4.1 Indication

The treatment of moderate to severe pain.

4.2 Posology and 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 adolescents aged 12 years and over

100-200 mg tramadol hydrochloride twice daily (corresponding to 200 – 400 mg of tramadol hydrochloride/day), morning and evening administration recommended.

The smallest effective analgesic dose should always be used. Daily doses of 400 mg of active substance must not be exceeded, unless exceptional medical reasons require so. A minimum interval of 8 hours must be respected between administrations.

Paediatric population

Tramadol Capsule 50 mg is not suitable for use in children below 25 kg body weight which in general does not allow for individualized dosage in children below 12 years of age.

Consequently, a more suitable form of administration should be used.

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 tramadol is delayed. In these patient's prolongation of the dosage intervals should be carefully considered according to the patient's requirements.

Method of administration

The prolonged-release capsule, hard, must be swallowed whole with sufficient liquid, irrespective of mealtimes.

4.3 Contraindication

Tramadol capsules are contraindicated:

- in hypersensitivity to the active substance.
- in acute intoxication with alcohol, hypnotics, analgesics, opioids, or other psychotropic medicinal products).
- in patients who are receiving MAO inhibitors or who have taken them within the last 14 days.
- in patients with epilepsy not adequately controlled by treatment.
- 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 Warning & precautions for use

Tramadol may only be used with particular caution in opioid-dependent patients, patients with head injury, shock, a reduced level of consciousness of uncertain origin, disorders of the respiratory centre or function, increased intracranial pressure.

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

Concomitant use of Tramadol and sedating medicinal products such as benzodiazepines or related substances, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedating medicinal products should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Tramadol concomitantly with sedating medicinal products, the lowest effective dose of tramadol should be used, and the duration of concomitant 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.

Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of tramadol exceed the recommended upper daily dose limit (400 mg). In addition, tramadol may increase the seizure risk in patients taking other medicinal products that lowers the seizure threshold (see section 4.5). Patients with epilepsy or those susceptible to seizures should be only treated with tramadol if there are compelling circumstances.

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.

Sleep-related breathing disorders
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.

Drug dependence, tolerance and potential for abuse
For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).
Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.
A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.
Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.
Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.
Patients should be closely monitored for signs of misuse, abuse, or addiction.
The clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome
Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with Tramadol.
Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.
The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.
If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Hyperalgesia
Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance.

Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.
Tramadol is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms.

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.

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 concomitant use of opioids with sedating medicinal products such as benzodiazepines or related substances increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect.
The dose of Tramadol and the duration of the concomitant use should be limited :
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.
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. 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.

4.6 **Fertility, Pregnancy and lactation**

Pregnancy

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.
If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.
Tramadol - administered before or during birth - does not affect uterine contractility.
Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breast-feeding

Administration to nursing women is not recommended as Tramadol may be secreted in breast milk and may cause respiratory depression in the infant. Alternatively, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not necessary following a single dose of tramadol.
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.

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**

Not available

4.8 **Undesirable effects**

The undesirable effects are classified into system organ classes and their frequency is classified as follows: Very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

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

Metabolism and nutrition disorders

Not known: hypoglycaemia

Rare:	changes in appetite
Psychiatric disorders	
Rare:	Hallucinations, confusion, sleep disturbance, anxiety and nightmares. Psychic side-effects may occur following administration of tramadol, 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 (mostly reduced, occasionally increased) and changes in cognitive and sensorial ability (e.g. decision behaviour, perception disorders). Dependence may occur.
Nervous system disorders	
Very common:	Dizziness.
Common:	Headache, somnolence.
Rare:	Changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform convulsions, abnormal coordination, involuntary muscle contractions, syncope. If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly (see section 4.5), 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 (see sections 4.4 and 4.5).
Not known:	speech disorders, serotonin syndrome
Eye disorders	
Rare:	Blurred vision, miosis, mydriasis..
Cardiac disorders	
Uncommon:	Cardiovascular regulation (palpitations, tachycardia, postural hypotension or cardiovascular collapse). These adverse effects may occur especially in connection with intravenous administration and if the patient is experiencing physical stress.
Rare:	Bradycardia, increased blood pressure.
Vascular disorder	
Uncommon:	cardiovascular regulation (postural hypotension or cardiovascular collapse). These adverse reactions may occur especially on intravenous administration and in patients who are physically stressed.

Respiratory, thoracic and mediastinal disorders

Rare:	Dyspnoea
Frequency not known:	Worsening of asthma has been reported, though a causal relationship has not been established, Hiccups.

Gastrointestinal disorders

Very common:	Nausea.
Common:	Vomiting, constipation, dry mouth.
Uncommon:	Retching; gastrointestinal irritation (a feeling of pressure in the stomach, bloating), diarrhoea.

Hepatobiliary disorders

Frequency not known:	In a few isolated cases an increase in liver enzyme values has been reported in a temporal connection with the therapeutic use of tramadol.

Skin and subcutaneous tissue disorders

Common:	Sweating.
Uncommon:	Dermal reactions (e.g. pruritus, rash, urticaria).

Musculoskeletal and connective tissue disorders

Rare:	Motorial weakness.

Renal and urinary disorders

Rare:	Micturition disorders (difficulty in passing urine and urinary retention).

General disorders

Common:	fatigue
Rare:	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 (i.e. confusion, delusions, depersonalization, derealization, paranoia).

Drug dependence

Repeated use of Tramadol can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

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

Serotonin syndrome has also been reported.

Treatment

The general emergency measures apply. Keep open the respiratory tract (aspiration), maintain respiration and circulation depending on the symptoms. The stomach is to be emptied by vomiting (conscious patient) or gastric irrigation. 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: Analgesics, other opioids.

ATC Code: N02AX02

Mechanism of action

Tramadol is a centrally-acting opioid analgesic. It is a non-selective pure agonist at μ, δ, and κ opioid receptors with a higher affinity at the μ receptors. Other mechanisms that contribute to its analgesic effect are inhibition of neuronal re-uptake of noradrenaline as well as increased serotonin release.

Clinical efficacy and safety

Tramadol has an antitussive effect. In contrast to morphine, tramadol in analgesic doses has no respiratory depression effect over a wide range and no effect on gastrointestinal motility. It has only a slight effect on the cardiovascular system.

Tramadol potency is given as 1/10 to 1/6 of that for morphine.

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

Following oral use tramadol absorption is greater than 90%. Absolute average bioavailability is 70%, irrespective of concurrent food intake. The difference between available absorbed and unmetabolized tramadol can be explained by the fact that there is only slight first-pass metabolism. First-pass metabolism following oral administration is 30% at most.

Distribution

Following oral use (50 mg) , peak plasma concentrations (Cmax) detectable within 45 minutes within a mean Cmax of 280 to 208mcg/L and Tmax of 1.6 to 2h. Tramadol has high tissue affinity (Vd, β = 203 ± 40 l). Serum protein binding is approximately 20%.

Tramadol crosses the blood-brain barrier and the placenta. Very slight amounts of the drug together with its O-demethyl derivative are found in maternal milk (0.1% and 0.02% of the administered dose, respectively).

Biotransformation

In humans, tramadol is essentially metabolized by N- and O-demethylation as well as by conjugation of the O-demethylation products with glucuronic acid. Only O-demethyl tramadol is pharmacologically active. There are considerable quantitative interindividual variations as regards the other metabolites. 11 metabolites have been found in urine to date. According to results of animal experiments, O-demethyl tramadol exceeds the potency of the parent substance by a factor of 2 to 4. Its half-life (t½ β) (6 healthy volunteers) is 7.9 hours (ranging between 5.4 to 9.6 hours) and is similar to that of tramadol.

Inhibition of the isoenzymes CYP3A4 and/or CYP2D6 involved in the biotransformation of tramadol can influence the plasma concentration of tramadol or that of its active metabolites.

Tramadol and its metabolites are almost completely excreted via the kidneys. Cumulative urinary excretion is 90% of the total radioactivity of the administered dose. Tramadol half-life may be slightly prolonged in patients with impaired liver or kidney function. Elimination half-lives of 13.3 ± 4.9 hours (tramadol) and of 18.5 ± 9.4 hours (O-demethyl tramadol) and in extreme cases of 22.3 and 36 hours, respectively have been determined in patients with cirrhosis of the liver. Elimination half-lives of 11 ± 3.2 hours and 16.9 ± 3 hours, and in extreme cases of 19.5 hours and 43.2 hours, respectively have been determined in patients with renal insufficiency (creatinine clearance < 5 ml/min).

Elimination

The elimination half-life (t½ β) of tramadol is about 6 hours, irrespective of the method of administration. In patients over 75 years of age, elimination half-life may be prolonged by a factor of approx. 1.4.

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, nonsignificant 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 Exciipents

- Corn Starch
- Lactose

- Talc Powder
- Magnesium Sterate

6.2 **Incompartibilities**
NOT APPLICABLE

6.3 **Shelf life**
36 months

6.4 **. Special precaution for Storage**

Do not store above 30°C.

6.5 **. Nature and contents of container**
1 strips of alu pvc blister of 10 capsules in a carton along with insert.

6.6 Special precaution for disposal & other handling : Not Available

7.0 **. Manufacturer**

KCH CONSUMER HEALTHCARE LTD
1-6 KCH Close, Off Bolanle Ambode Expressway, Poka,Epe, Lagos