Summary of product characteristics

1. **Name of the medicinal product**
   TRADOL 50 Capsules

2. **Qualitative and quantitative composition:**

Sr. No.	Ingredients	Specification	Actual Qty (in mg)/cap	Overages	Actual Qty (in mg) with Overages	Actual Qty for 510000 capsules (in kg)	Function
1.	Tramadol Hydrochloride	BP	50.00	10%	55.00	28.05	Active
2.	Di-calcium Phosphate	BP	10.00	--	10.00	5.10	Diluent
3.	Maize Starch	BP	49.02	--	49.02	25.00	Disintegrant
4.	Sodium Lauryl Sulphate	BP	2.00	--	2.00	1.02	Lubricant
5.	Sodium Starch Glycolate	BP	10.00	--	10.00	5.10	Disintegrant
6.	Purified Talc	BP	25.98	--	25.98	13.25	Diluent
7.	Magnesium Stearate	BP	2.00	--	2.00	1.02	Lubricant
8.	Colloidal Anhydrous Silica	BP	1.00	--	1.00	0.51	Absorbent
9.	Dark Blue cap/White Body Size '4' hard Gelatin Capsules	IH	--	3%		525,300	Capsule Shell
	Net content				155.00		
	Av. Weight of Empty Capsule				40.00		
	Av. Weight of filled Capsule				195.00		

Where, BP: British Pharmacopoeia
IH: In-house Specification

3. **Pharmaceutical form:** Oral dosage form

4. Clinical Particular

4.1. Therapeutic indicators

Management (treatment and prevention) of moderate to severe pain.

4.2 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 analgesically effective dose should generally be selected. Daily doses of 400mg active substance should not be exceeded, except in special clinical circumstances.

Unless otherwise prescribed, Tramadol Hydrochloride Capsules should be administered as
follows: Adults and adolescents aged 12 years and over Acute Pain: An initial dose of 100mg is usually necessary. This can be followed by doses of 50 or 100mg not more frequently than 4 hourly, and duration of therapy should be matched to clinical need.
Pain Associated with Chronic Conditions: Use an initial dose of 50mg 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.

Children under 12 years

Tramadol Hydrochloride Capsules are not suitable for children below the age of 12 years.

Geriatric patients

The usual dosages may be used although it should be noted that in volunteers aged over 75 years the elimination half-life of tramadol was increased by 17% following oral administration. 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 extended according to the patient's requirements,

Renal insufficiency/dialysis

The elimination of tramadol may be prolonged/ delayed. In these patients, prolongation of the dosage intervals should be carefully considered according to the patient's requirements. The usual initial dosage should be used. For patients with creatinine clearance <30ml/min, the dosage interval should be increased to 12 hours. Tramadol is not recommended for patients with severe renal impairment (creatinine clearance <10ml/min).

Hepatic impairment

The elimination of tramadol may be prolonged/ delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements. The usual initial dosage should be used but in severe hepatic impairment the dosage interval should be increased to 12 hours. As tramadol is only removed very slowly by haemodialysis or haemofiltration, post- dialysis administration to maintain analgesia is not usually necessary. In these patients the dosage intervals should be carefully considered according to the patients requirements.

Method of administration

For oral administration.
The capsules are to be taken whole, not divided or chewed, with sufficient liquid, with or without food.

Duration of administration

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.

Treatment goals and discontinuation

Before initiating treatment with Tramadol a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed

together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with tramadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered.

4.3 Contraindication

Tramadol is contraindicated:
- in hypersensitivity to tramadol or any of the excipients.
- in acute intoxication with alcohol, hypnotics, analgesics, opioids, or psychotropic medicinal products,
- in patients with epilepsy not adequately controlled by treatment,
- for use in narcotic withdrawal treatment
- in patients who are receiving MAO inhibitors or who have taken them within the last 14 days.

4.4 Special warning and precautions for use

Tramadol may only be used with particular caution in opioid-dependent patients, patients with head injury, convulsive disorders, shock, a reduced level of consciousness of uncertain origin, disorders of the respiratory center or function, increased intracranial pressure, severe impairment of hepatic and renal function.
In patients sensitive to opiates the product should only be used with caution. Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered (see section 4.5), or if the recommended dosage is significantly exceeded (see section 4.9) as the possibility of respiratory depression cannot be excluded in these situations. Concomitant use of Tramadol and sedating medicinal products such as benzodiazepines or related products may result in respiratory depression, sedation, coma or death. Concomitant prescribing of such products should only be undertaken if alternative treatment options are not possible. If concomitant prescribing is the only option, the lowest effective dose of Tramadol should be used, and duration of concomitant treatment should be as short as possible.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Slow metaboliser status for CYP3A4 and/or CYP2D6 may present a risk for tramadol toxicity (Pharmacokinetic properties).
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. 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.

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

At therapeutic doses withdrawal symptoms have been reported at a reporting frequency of 1 in 8,000. Reports of abuse and dependence have been less frequent. Because of this potential the clinical need for continued analgesic treatment should be reviewed regularly.

Tolerance and opioid use disorder (abuse and dependence)

Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as Tramadol. Repeated use of Tramadol can lead to opioid use disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of Tramadol may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with Tramadol and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like
benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.
Tramadol is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms.

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 products increases the risk of respiratory depression, sedation, coma and death because of additive CNS depressant effect. The dose of Tramadol and the duration of the concomitant use should be limited.
The concomitant use of Tramadol with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death.
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. Therefore no alteration of the tramadol dosage regimen is recommended for patients receiving chronic cimetidine therapy.
Simultaneous or previous administration of carbamazepine (enzyme inducer) may reduce the analgesic effect and shorten the duration of action. There is a theoretical possibility that tramadol could interact with lithium due to their respective mechanisms 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 reuptake inhibitors (SSRIs), serotonin- norepinephrine reuptake inhibitors (SNRIs), tricyclic anti-
depressants, anti-psychotics and other seizure threshold lowering medicinal products (such as bupropion, mirtazapine, tehrahydrocannabinol) 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. 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 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 tramadol in patients with postoperative pain

4.6 Pregnancy and Lactation

Pregnancy

Animal studies with tramadol revealed at very high doses effects on organ development, ossification and neonatal mortality. 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 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

During lactation approximately 0.1 % of the maternal dose is secreted in breast milk. In the immediate post-partum period, for maternal oral daily dosage up to 400 mg, this corresponds to a mean amount of tramadol ingested by breast-fed infants of 3% of the maternal weight-adjusted dosage. For this reason tramadol should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not necessary following a single dose of tramadol.

Fertility

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

4.7 Effects on ability to drive and use machines

Tramadol may cause somnolence and dizziness and therefore may impair the reactions of drivers and machine operators 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.
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:
o The medicine has been prescribed to treat a medical or dental problem and
o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
o It was not affecting your ability to drive safely.

4.8 Undesirable effects

The most commonly reported adverse reactions are nausea and dizziness, both occurring in more than 10 % of patients. The frequencies are defined as follows: Very common: ≥1/10

Common: ≥1/100, <1/10 Uncommon: ≥1/1000, <1/100 Rare: ≥1/10 000, <1/1000 Very rare: <1/10 000

Not known: cannot be estimated from the available data Cardiovascular disorders: Uncommon: cardiovascular regulation (palpitation, tachycardia). These adverse reactions may occur especially on intravenous administration and in patients who are physically stressed.

Rare: bradycardia,

Investigations;

Rare: increase in blood pressure Vascular disorders

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

Nervous system disorders:

Very common: dizziness

Common: headache, somnolence

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

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

Psychiatric disorders:

Rare: hallucinations, confusion, sleep disturbance, delirium, anxiety, dysphoria 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 incognitive and sensorial capacity (e.g. decision behaviour, perception disorders).

Dependence may occur.

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, de-personalisation, derealisation, paranoia).

Eye disorders:

Rare: miosis, blurred vision, mydriasis

Respiratory, thoracic and mediastinal disorders:

Rare: dyspnoea, respiratory depression, Worsening of asthma has been reported, though a causal relationship has not been established. If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly (see section 4.5), respiratory depression may occur.

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 (sweating profusely)
Uncommon: dermal reactions (e.g. pruritus, rash, urticaria)
Musculoskeletal and connective tissue disorders:
Rare: motorial weakness
Hepatobiliary disorders:
In a few isolated cases an increase in liver enzyme values has been reported in a temporal connection with the therapeutic use of tramadol.
Renal and urinary disorders:
Rare: micturition disorders (dysuria and urinary retention)
Metabolism and nutrition disorders:
Rare: changes in appetite
Not known: hypoglycaemia
Immune system disorders
Rare: allergic reactions including dyspnoea, wheezing, bronchospasm, angioneurotic oedema and anaphylaxis have been reported.
General disorders:
Common: fatigue
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.

4.9 Overdose
Symptoms
In principle, on intoxication with tramadol symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include in particular miosis, vomiting, and cardiovascular collapse, consciousness disorders sedation up to coma, convulsions / seizures 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. Fits can be controlled with diazepam. 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 hemofiltration. Therefore treatment of acute intoxication with tramadol with haemodialysis or hemofiltration alone is not suitable for detoxification.

5. Pharmacological Properties
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: other opioids;
ATC-code N 02 AX 02
Tramadol is a centrally acting opioid 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 antitussive effect. It is a non-selective pure agonist at μ, δ, and κ opioid receptors with a higher affinity for the μ receptor. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release.
Tramadol has an antitussive effect. In contrast to morphine, analgesic doses of tramadol 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 tramadol is reported to be 1/10 (one tenth) to 1/6 (one sixth) that of 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 Pharmacokinetics 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 C max of 280 to 208 mcg/L and T max 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

Di-calcium Phosphate, Maize Starch, Sodium Lauryl Sulphate, Sodium Starch Glycolate, Purified Talc, Magnesium Stearate, Colloidal Anhydrous Silica, Dark blue cap/white body Size '4' hard gelatin capsules.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precaution for storage

Store below 30°C. Protected from light.
Keep all medicines out of reach of children.

6.5 Nature and content of container

Primary packing: 10 capsules packed in an ALU-PVC blister
Secondary packing: Such 10 blisters packed in one carton with insert.
Tertiary packing: Sleeves individual carton. Such carton is packed in a 7-ply shipper sealed with BOPP tape.

.6.6 Special precaution for disposal and other handling

None

7 Marketing authorisation holder and manufacturing site addresses

Marketing authorisation holder:
MASTER PHARMACEUTICALS LIMITED
AE-0249-3162, TIKROM-KUMASI EJISU-JUABEN
Ghana.

Manufacturer:
ZAIN PHARMA LTD.
Plot No: 209/13741, Colchester Park,
Go-Down No.1, 2, 3, Off Mombasa Road,
Behind Nice And Lovely House,
P.O. Box: 100167-00101, Nairobi, Kenya

8 Marketing authorisation number
FDA/SD.255-040585

9. Date of first authorisation or renewal
4/11/2025

10. Date of Revision of the Test
9th July,2025