Summary of Product Characteristics

1. Name of the medicinal product
Domadol (Tramadol Hydrochloride) 50 mg Injection

2. Qualitative and quantitative composition
Each mL contains Tramadol Hydrochloride ……50 mg
Water for injection……...qs
For the full list of excipients, see Section 6.1.

3. Pharmaceutical form
Clear, colorless liquid free from particles

4. Clinical particulars
4.1 Therapeutic indications

Treatment of moderate to severe pain.

4.2 Posology and method of administration

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with tramadol in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).
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 400 mg tramadol hydrochloride should not be exceeded, except in special clinical circumstances.
Unless otherwise prescribed, Tramadol hydrochloride 50 mg/ml solution for injection or infusion should be administered as follows:

Adults and adolescents above the age of 12 years:
The usual dose is 50 or 100mg 4-6 hourly by the intravenous or intramuscular route. Dosage should be adjusted according to pain severity and response.
Intravenous injections must be given slowly over 2-3 minutes.
For post-operative pain administer an initial bolus of 100mg. 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.

Children
Tramadol hydrochloride 50 mg/ml solution for injection or infusion is not suitable for children below the age of 12 years.

Geriatric patients
A dose adjustment is not usually necessary in elderly 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 Insufficiency
In patients with renal and/or hepatic insufficiency the elimination of tramadol is delayed. In these patients' prolongation of the dosage intervals should be carefully considered according to the patient's requirements.

Method of administration
Tramadol hydrochloride 50 mg/ml solution for injection or infusion may be administered intramuscularly, by slow intravenous injection, or diluted in solution (see Section 6.6) for administration by infusion or patient controlled analgesia.

Duration of administration
Tramadol hydrochloride 50 mg/ml solution for injection or infusion should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with Tramadol hydrochloride 50 mg/ml solution for injection or infusion 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.

4.3 Contraindications

Tramadol hydrochloride 50 mg/ml solution for injection or infusion is contraindicated
- in patients who have previously shown hypersensitivity to the active substance tramadol or to any of the excipients listed in section 6.1.
- in patients suffering from acute intoxication with alcohol, hypnotics, analgesics, opioids, or psychotropic medicinal products.
- in patients who are receiving monoamine oxidase (MAO) inhibitors or who have taken them within the last 14 days (see section 4.5)
- in patients with epilepsy not adequately controlled by treatment.
- for use in narcotic withdrawal treatment.

4.4 Special warnings and precautions for use

Tramadol hydrochloride 50 mg/ml solution for injection or infusion 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.
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.

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 only be treated with tramadol if there are compelling circumstances.

<u>Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs</u>
Concomitant use of Tramadol hydrochloride 50 mg/ml solution for injection or infusion and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Tramadol hydrochloride 50 mg/ml solution for injection or infusion concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

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.

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

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 hydrochloride 50 mg/ml solution for injection or infusion.

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.

Tramadol hydrochloride 50 mg/ml solution for injection or infusion is not a suitable substitute in opioid dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms.

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.

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.

Serotonin syndrome
Serotonin syndrome, a potentially life-threatening condition, has been reported in patients receiving tramadol in combination with other serotonergic agents or tramadol alone (see sections 4.5, 4.8 and 4.9).

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose escalations.
Symptoms of serotonin syndrome may include mental status changes, autonomic instability, neuromuscular abnormalities and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms. Withdrawal of the serotonergic drugs usually brings about a rapid improvement.

4.5 Interaction with other medicinal products and other forms of interaction

Tramadol hydrochloride 50 mg/ml solution for injection or infusion should not be combined with MAO inhibitors (see section 4.3).

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 hydrochloride 50 mg/ml solution for injection or infusion.

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 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.

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 syndrome, a potentially life-threatening condition (see sections 4.4 and 4.8).

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 (see section 4.8).

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. The administration of Tramadol hydrochloride 50 mg/ml solution for injection or infusion with other centrally depressant medicinal products, including alcohol, may potentiate the CNS effects (see section 4.8).

Sedative medicines such as benzodiazepines or related drugs
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

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. Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available. Tramadol - administered before or during birth - does not affect uterine contractility.

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 hydrochloride 50 mg/ml solution for injection or infusion should not be used in pregnant women.

Breast-feeding
Approximately 0.1 % of the maternal dose is excreted into the 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 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.

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

Even when taken according to instructions, Tramadol hydrochloride 50 mg/ml solution for injection or infusion may cause effects such as somnolence and dizziness and therefore may impair a patient's ability to drive safely or operate machinery. This applies particularly in conjunction with alcohol and other psychotropic substances. Patients should, therefore, not drive or operate machinery.

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 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.

Metabolism and nutrition disorders:
Rare: changes in appetite
Not known: hypoglycaemia

Respiratory, thoracic and mediastinal disorders:
Rare: respiratory depression, dyspnoea
Not known: hiccups

If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly (see section 4.5), respiratory depression may occur.

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

Nervous system disorders:
very common : dizziness
common : headache, somnolence
rare : changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope.
not known: serotonin syndrome, speech disorders
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).

Psychiatric disorders:
rare : hallucinations, confusion, sleep disturbance, delirium, anxiety and nightmares. Psychological adverse reactions may occur following administration of Tramadol hydrochloride 50 mg/ml solution for injection or infusion 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.

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, depersonalisation, derealisation, paranoia).
Not known: Drug dependence (see section 4.4)

Eye disorders:
rare : miosis, mydriasis, blurred vision

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 tissue disorders:
common : sweating
*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 (difficulty in passing urine, dysuria and urinary retention)

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

General disorders and administration site conditions:
common : fatigue
Uncommon: drug withdrawal syndrome

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system (see details below).

Paper based reporting: TMDA yellow card
Online reporting: https://sqrt.tmda.go.tz/
USSD reporting: send a simple short text message to report any suspected Adverse Drug Reaction by dialing *152*00# and follow the instructions

4.9 Overdose

Symptoms
Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.
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 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.

Tramadol is minimally eliminated from the serum by haemodialysis or haemo-filtration. Therefore, treatment of acute intoxication with Tramadol hydrochloride 50 mg/ml solution for injection or infusion with haemodialysis or haemofiltration alone is not suitable for detoxification.

5. Pharmacological properties
5.1 Pharmacodynamic properties

Analgesic, ATC code: N02AX02
Tramadol is a centrally acting analgesic which possesses opioid agonist properties. Tramadol consists of two enantiomers, the (+)-isomer is predominantly active as an opioid with preferential activity for the μ-receptor. The (-)-isomer potentiates the analgesic effect of the (+)-isomer and is active as an inhibitor of noradrenaline and serotonin uptake thereby modifying the transmission of pain impulses.

Tramadol also has an antitussive action. At the recommended dosages, the effects of tramadol given orally on the respiratory and cardiovascular systems appear to be clinically insignificant. The potency of tramadol is reported to be 1/10th to 1/6th 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 (see section 4.2).

5.2 Pharmacokinetic properties

a) General
The mean absolute bioavailability after intramuscular administration was found to be 100%.
The distribution of tramadol following intravenous administration is rapid and in two phases with different half-lives of 0.31 ± 0.17 hours (initial rapid phase) and 1.7± 0.4 hours (slower phase) respectively.

After intravenous administration of 100 mg tramadol, the serum concentration was 613 ± 221 ng/ml at 15 minutes post dosing and 409 ± 79 ng/ml at 2 hours post dosing. Tramadol has a high tissue affinity with an apparent volume of distribution of 203 L after intravenous dosing in healthy volunteers.

Tramadol undergoes hepatic metabolism with approximately 85% of an intravenous dose being metabolised in young healthy volunteers. 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-desmthyltramadol is more potent than the parent substance by the factor 2-4. Its half life t½β (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 cytochrome P450 isoenzymes, CYP3A4 and CYP2D6 involved in the metabolism of tramadol, may affect the plasma concentration of tramadol or its active metabolite.

Tramadol is essentially excreted via the kidneys. The mean elimination half-life of tramadol following intravenous administration is 5-6 hours. Total clearance of tramadol was 28.0 L/h following intravenous administration.

b) Characteristics in patients
Effect of age: Tramadol pharmacokinetics show little age-dependence in volunteers up to the age of 75 years. In volunteers aged over 75 years, the terminal elimination half-life was 7.0 ± 1.6 h compared to 6.0 ± 1.5 h in young volunteers after oral administration. Effect of hepatic or renal impairment: As both tramadol and its pharmacologically active metabolite, O-desmethyl tramadol, are eliminated both metabolically and renally, the terminal half-life of elimination (t½) may be prolonged in patients with hepatic or renal dysfunction. However, the increase in t½ is relatively small if either excretory organ is functioning normally. In liver cirrhosis patients, the mean t½ of

tramadol was 13.3 ± 4.9 hours. In patients with renal failure (creatinine clearance < 5 mL/min) the t½ of tramadol was 11.0 ± 3.2 hours and that of M1 was 16.9 ± 3.0 hours. Extreme values observed to date are 22.3 hours (tramadol) and 36.0 hours (M1) in liver cirrhosis patients and 19.5 hours (tramadol) and 43.2 hours (M1) in renal failure patients.

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

Citric Acid Anhydrous
Sodium Citrate
Water for Injection

6.2 Incompatibilities

Precipitation will occur if Tramadol hydrochloride 50 mg/ml solution for injection or infusion is mixed in the same syringe with injections of diazepam, diclofenac sodium, indomethacin, midazolam and piroxicam.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

A transparent “snap-off” 1 mL USP Type I glass ampoule with blue ring constriction. 5 such ampoules are packed in a blister

6.6 Special precautions for disposal and other handling

Based on described observations Tramadol 50 mg/ml solution for injection or infusion is physically and chemically compatible for up to 24 hours with water for injections (WFI), sodium chloride solution for injection 0.9% and glucose solution for injection 5% at given concentrations. Obtained results show no necessity for cold storage.

The prepared infusion solution should be made immediately before use.

7. Marketing authorisation holder

Unichem Laboratories Limited
Baddi Unit II and Ghaziabad
India

8. Marketing authorisation number(s)

TAN 20 HM 0114

9. Date of first authorisation

July 09, 2020

10. Date of revision of the text

November 05, 2023