Tramadis 100 MG/2ML

Summary of Product Characteristics

1. Name of the medicinal product

Tramadis 100 MG/2ML solution for injection

2. Qualitative and quantitative composition

1 ml of solution contains 50 mg of tramadol hydrochloride.

One ampoule (2 ml) contains 100 mg of tramadol hydrochloride.

Excipients with known effect :

One ampoule (2 ml) contains 8.29 mg sodium acetate trihydrate sodium acetate

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for injection/infusion.

Box of 5 ampoules.

Limpid colourless liquid.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of moderate to severe pain.

4.2 Posology and method of 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. The total daily dose of 400 mg tramadol should not be exceeded, except in special clinical circumstances (for example, in case of cancer pain or postoperative severe pain).

Unless otherwise prescribed, Tramadis should be administered as follows:

Adults and adolescents above the age of 12 years

Depending on the intensity of pain, 50–100 mg of tramadol (corresponds to 1-2 ml of Tramadis is administered every 4–6 hours. The total daily dose of 400 mg should not be exceeded.

Elderly patients

A dose adjustment is not usually necessary in patients up to 75 years without clinically manifest hepatic or renal insufficiency. In patients over 75 years elimination may be prolonged. Therefore, if necessary the dosage interval is to be extended according to individual 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.

Paediatric population

Tramadis should not be used in children under 1 year of age.

For children up to the age of 12, the single dose of tramadol is 1-2 mg per kg body weight. The lowest effective dose for analgesia should generally be selected. The total daily dose must not exceed the lowest of these doses – 8 mg/kg body weight or 400 mg of the active substance.

Method of administration

Intravenous (solution is to be injected slowly (1 ml (50 mg of tramadol hydrochloride) per minute)), intramuscular or subcutaneous injection. Tramadis may also be diluted in solution for infusion (for example, 0.9% sodium chloride or 5% glucose solution) and infused.

For instructions on dilution of the medicinal product before administration, see section 6.6.

Duration of administration

Tramadis should under no circumstances be administered for longer than absolutely necessary. If long-term pain

treatment with Tramadis 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.

4.3 Contraindications

- Hypersensitivity to the active substance and/or to any of the excipients listed in section 6.1
- Acute intoxication with alcohol, hypnotics, analgesics, opioids, or other psychotropic medicinal products
- Patients who are receiving MAO inhibitors or who have taken them within the last 14 days (see section 4.5)
- Patients with epilepsy not adequately controlled by treatment
- For use in narcotic withdrawal treatment.

4.4 Special warnings and precautions for use

CYP2D6 metabolism

Tramadis 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

Tramadis 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.

Tramadis 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 a dose of tramadol exceeds the recommended daily dose (400 mg). Tramadis may increase the seizure risk in patients taking other medicinal products that lowers the seizure threshold (see section 4.5). In patients with epilepsy or those susceptible to seizures, tramadol may only be used when absolutely necessary.

Tolerance, psychic and physical dependence may develop, especially after long-term use. Therefore, in patients with a tendency to drug abuse or dependence, treatment with tramadol should only be carried out for short periods under strict medical supervision.

When a patient no longer requires therapy with tramadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

This medicinal product is not suitable as a substitute in opioid-dependent patients. Although tramadol is an opioid agonist, it cannot suppress morphine withdrawal symptoms.

Tramadis contains less than 1 mmol (23 mg) of sodium in one ampoule.

4.5 Interaction with other medicinal products and other forms of interaction

MAO inhibitors

Tramadis should not be used in combination 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 affecting the central nervous system, respiratory and cardiovascular function have been observed. The same interactions with MAO inhibitors cannot be ruled out during treatment with Tramadis.

Cimetidine

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.

Carbamazepine

Simultaneous or previous administration of carbamazepine (enzyme inducer) may reduce the analgesic effect and shorten the duration of action.

CNS-active agents

Concomitant administration of Tramadis with other centrally depressant medicinal products including alcohol may potentiate the CNS effects (see section 4.8).

Tramadis 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, 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 serotonergic drugs usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

Coumarin derivatives

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.

CYP3A4 inhibitors

Other active substances known to inhibit CYP3A4, such as ketoconazole and erythromycin, might inhibit the metabolism of tramadol (N- demethylation) and 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).

Ondansetron

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

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

Tramadis – 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. Prolonged use during pregnancy may lead to neonatal withdrawal symptoms.

Breastfeeding

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. 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

Even when taken according to instructions, Tramadis may cause effects such as somnolence and dizziness and therefore may impair the reactions of drivers and machine operators. This applies particularly in conjunction with alcohol and other psychotropic substances.

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 :

- 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

The side effects mentioned below are listed according to MedDRA system organ classification. The frequencies are ranked according to the following convention : 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), not known (cannot be estimated from the available data).

The most commonly reported adverse reactions are nausea and dizziness. These occur in more than 10% of patients.

Immune system disorders

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

Cardiac disorders

Uncommon: effect on cardiovascular regulation (palpitations, 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: effect on 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.

Convulsions occurred mainly after administration of high doses of tramadol or after concomitant treatment with medicinal products lowering the seizure threshold (see sections 4.4 and 4.5).

Metabolism and nutrition disorders

Rare: changes in appetite.

Not known: hypoglycaemia.

Psychiatric disorders

Rare: hallucinations, confusion, sleep disturbance, delirium, anxiety and nightmares.

Psychic adverse reactions may occur following administration of Tramadis 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).

Drug dependence may occur. Symptoms of drug withdrawal syndrome, similar to those occurring during opiate withdrawal, may occur. These include: 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).

Eye disorders

Rare: miosis, mydriasis, blurred vision.

Respiratory, thoracic and mediastinal disorders

Rare: respiratory depression, dyspnoea.

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.

Gastrointestinal disorders

Very common: nausea.

Common: constipation, dry mouth, vomiting.

Uncommon: retching, gastrointestinal discomfort (a feeling of pressure in the stomach, bloating), diarrhoea.

Hepatobiliary disorders

Very rare: 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: hyperhidrosis.

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

Musculoskeletal and connective tissue disorders

Rare: muscular weakness.

Renal and urinary disorders

Rare: micturition disorders (dysuria and urinary retention).

General disorders and administration site conditions

Common: fatigue.

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. Healthcare professionals are asked to report any suspected adverse reactions via the National Center of Pharmacovigilance (NCPV).

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.

Treatment

The general emergency measures should be taken. 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 or prolonged-release formulations.

Tramadis is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore treatment of acute intoxication with Tramadis 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

Tramadis is a centrally acting opioid analgesic. 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.

Tramadis 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 to 1/6 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

After intramuscular administration in humans, tramadol is absorbed rapidly and completely: the mean peak serum concentration (C_{max}) is reached after 45 minutes, and bioavailability is almost 100%.

Tramadis has a high tissue affinity ($V_{d,\beta}$ = 203 ± 40 l). It has a plasma protein binding of about 20%.

Tramadis 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).

The inhibition of one or both types of the isoenzymes CYP3A4 and CYP2D6 involved in the biotransformation of Tramadis may affect the plasma concentration of tramadol or its active metabolite.

Tramadis and its metabolites are almost completely excreted via the kidneys. Cumulative urinary excretion is 90% of the total radioactivity of the administered dose. Elimination half-life $t_{1/2,\beta}$ 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 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.

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, 11 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, $t_{1/2,\beta}$ (6 healthy volunteers) is 7.9 h (range 5.4 – 9.6 h) and is approximately that of tramadol.

Tramadis 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 in rats 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 15mg/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

Sodium acetate trihydrate

Water for injections

6.2 Incompatibilities

Tramadis should not be mixed with solutions for injection or infusion containing diclofenac, indomethacin, phenylbutazone, diazepam, midazolam, flunitrazepam and glyceryl trinitrate.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store away from light and heat

6.5 Nature and contents of container

Type I white neutral drawn glass silk-screen ampoules with breaking point (OPC) capacity :2 ml.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

Les laboratoires MédiS , Route de Tunis – Km 7 – BP 206 – 8000 Nabeul – Tunisie.

8. Marketing authorisation number(s)

9233281

9. Date of first authorisation/renewal of the autorisation

Date of first Authorisation: 13/06/2003
Date of first renewal: 12/06/2008
Date of second renewal: 12/06/2013
Date of third renewal: 12/06/2018

10. Date of revision of the text

03/2022