VERDOL (Tramadol Hydrochloride Injection 50mg/ml – 2ml)

1. Name of the finished Pharmaceutical Product

VERDOL (Tramadol Hydrochloride Injection)

1.1 Strength

50mg/ml – 2ml

1.2 Pharmaceutical form

Sterile Solution for Injection

2. Qualitative and Quantitative Composition

2.1 Qualitative declaration

Each ml contains: Tramadol Hydrochloride BP 50mg; Water for Injection BP q.s.

2.2 Quantitative declaration

Each ml contains: Tramadol Hydrochloride BP 50mg; Water for Injection BP q.s.

For full list of excipients see section 6.1.

3. Pharmaceutical form

A clear, colourless solution filled in a 2ml clear glass ampoule.

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, the injection 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 following 60 minutes, 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: not suitable for children below the age of 12 years.

Geriatric patients: 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; if necessary the dosage interval should be extended.

Renal insufficiency/dialysis and hepatic insufficiency: elimination of tramadol is delayed; prolongation of dosage intervals should be carefully considered.

Method of administration: 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: should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment is necessary, 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

- 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

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, or if the recommended dosage is significantly exceeded, as the possibility of respiratory depression cannot be excluded.

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

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs: may result in sedation, respiratory depression, coma and death. Concomitant prescribing should be reserved for patients for whom alternative treatment options are not possible, using the lowest effective dose and shortest possible duration. Patients should be followed closely for signs and symptoms of respiratory depression and sedation.

Sleep-related breathing disorders: opioids can cause central sleep apnoea (CSA) and sleep-related hypoxemia in a dose-dependent fashion; consider decreasing total opioid dosage in patients who present with CSA.

Adrenal insufficiency: opioid analgesics may occasionally cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy.

Drug dependence, tolerance and potential for abuse: prolonged use may lead to drug dependence (addiction), even at therapeutic doses; risks are increased with a history of substance misuse or mental health disorder. Additional support and monitoring may be necessary for patients at risk of opioid misuse. Patients may develop tolerance and should be closely monitored for signs of misuse, abuse, or addiction; clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome: a withdrawal strategy should be discussed before starting treatment. Withdrawal syndrome may occur upon abrupt cessation or dose reduction; when no longer required, the dose should be tapered gradually (which may take weeks to months). Withdrawal is characterised by restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations, and may include irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure and increased respiratory/heart rate. Tramadol is not a suitable substitute in opioid dependent patients and cannot suppress morphine withdrawal symptoms. Use during pregnancy risks neonatal withdrawal syndrome.

Hyperalgesia: may be diagnosed if the patient on long-term opioid therapy presents with increased pain, more diffuse and less defined than pre-existing pain; symptoms may resolve with a reduction of opioid dose.

CYP2D6 metabolism: tramadol is metabolised by CYP2D6; deficiency may result in inadequate analgesic effect, while ultra-rapid metabolisers risk 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, and in severe cases circulatory and respiratory depression which may be life threatening and very rarely fatal.

Population	Prevalence of ultra-rapid metabolisers
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: tramadol given post-operatively after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea has led to rare, but life-threatening adverse events; extreme caution and close monitoring for opioid toxicity, including respiratory depression, is required.

Children with compromised respiratory function: tramadol is not recommended for use in children in whom respiratory function might be compromised (neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures), as these factors may worsen symptoms of opioid toxicity.

Serotonin syndrome: a potentially life-threatening condition, has been reported in patients receiving tramadol in combination with other serotonergic agents or tramadol alone. If concomitant treatment with other serotonergic agents is clinically warranted, careful observation is advised, particularly during treatment initiation and dose escalations. Symptoms may include mental status changes, autonomic instability, neuromuscular abnormalities and/or gastrointestinal symptoms. If suspected, dose reduction or discontinuation should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Should not be combined with MAO inhibitors (see section 4.3). Life-threatening interactions on the central nervous system, respiratory and cardiovascular function have been observed with MAO inhibitors and the opioid pethidine within 14 days of use, and the same cannot be ruled out during treatment with tramadol.

Concomitant or previous administration of cimetidine (enzyme inhibitor) is unlikely to cause clinically relevant interactions. 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 SSRIs, 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 (SSRIs, SNRIs, MAO inhibitors, tricyclic antidepressants and mirtazapine) may cause serotonin syndrome, a potentially life-threatening condition.

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) and probably also of the active O-demethylated metabolite; clinical importance has not been studied.

In a limited number of studies, pre- or postoperative application of the antiemetic 5-HT3 antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain.

Administration with other centrally depressant medicinal products, including alcohol, may potentiate CNS effects.

Sedative medicines such as benzodiazepines or related drugs: concomitant use increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect; dose and duration of concomitant use should be limited.

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, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure 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 on the safety of tramadol in human pregnancy; it should not be used in pregnant women.

Breast-feeding: Approximately 0.1% of the maternal dose is excreted into the milk. For maternal oral daily dosage up to 400 mg, this corresponds to a mean amount ingested by breast-fed infants of 3% of the maternal weight-adjusted dosage. Administration to nursing women is not recommended; alternatively, breast-feeding should be discontinued during treatment.

Fertility: Post-marketing surveillance does not suggest an effect of tramadol on fertility; animal studies did not show an effect on fertility.

4.7 Effects on ability to drive and use machines

May cause somnolence and dizziness and therefore may impair a patient's ability to drive safely or operate machinery, particularly in conjunction with alcohol and other psychotropic substances. Patients should not drive or operate machinery.

This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. Patients should be told: the medicine is likely to affect their ability to drive; not to drive until they know how the medicine affects them; and that it is an offence to drive while under the influence of this medicine. However, they would not be committing an offence (called a 'statutory defence') if the medicine has been prescribed to treat a medical or dental problem, taken according to instructions, and was not affecting their ability to drive safely.

4.8 Undesirable effects

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

Frequency categories: 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 available data.

System Organ Class	Frequency	Reactions
Cardiovascular disorders	Uncommon	Palpitation, tachycardia (especially IV administration and physical stress)
	Rare	Bradycardia
Investigations	Rare	Increase in blood pressure
Vascular disorders	Uncommon	Postural hypotension or cardiovascular collapse (especially IV administration and physical stress)
Metabolism and nutrition disorders	Rare	Changes in appetite
	Not known	Hypoglycaemia
Respiratory, thoracic and mediastinal disorders	Rare	Respiratory depression, dyspnoea
	Not known	Hiccups
Nervous system disorders	Very common	Dizziness
	Common	Headache, somnolence
	Rare	Changes in appetite, paraesthesia, tremor, respiratory depression,

System Organ Class	Frequency	Reactions
		epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope
	Not known	Serotonin syndrome, speech disorders
Psychiatric disorders	Rare	Hallucinations, confusion, sleep disturbance, delirium, anxiety and nightmares
	Not known	Drug dependence
Eye disorders	Rare	Miosis, mydriasis, blurred vision
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting, constipation, dry mouth
	Uncommon	Retching; gastrointestinal irritation (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, increase in liver enzyme values has been reported in temporal connection with tramadol use
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

Worsening of asthma has been reported, though a causal relationship has not been established. Convulsions occurred mainly after administration of high doses or after concomitant treatment with medicinal products that lower the seizure threshold. Psychological adverse reactions, varying individually, may include changes in mood (usually elation, occasionally dysphoria), changes in

activity (usually suppression, occasionally increase), and changes in cognitive and sensorial capacity; dependence may occur. Withdrawal symptoms similar to opiate withdrawal may occur, including agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms; other very rare symptoms include panic attacks, severe anxiety, hallucinations, paraesthesias, tinnitus and unusual CNS symptoms (confusion, delusions, depersonalisation, derealisation, paranoia).

4.9 Overdose

Symptoms: Patients and their families/friends should be informed of the signs and symptoms of overdose and to seek immediate medical help if they occur. Symptoms similar to other centrally acting analgesics (opioids) are to be expected, 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: General emergency measures apply. Keep the respiratory tract open (aspiration!), maintain respiration and circulation depending on symptoms. The antidote for respiratory depression is naloxone; in animal experiments naloxone had no effect on convulsions, in which case diazepam should be given intravenously. Gastrointestinal decontamination with activated charcoal or gastric lavage is only recommended within 2 hours after oral tramadol intake (may be useful later for exceptionally large quantities). Tramadol is minimally eliminated from serum by haemodialysis or haemofiltration; these are not suitable as sole treatments 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 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 from neonate to 17 years of age, for pain after surgery, tooth extractions, fractures, burns and traumas, and other painful conditions

requiring 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 was superior to placebo, and superior or equal to paracetamol, nalbuphine, pethidine or low dose morphine. The safety profile of tramadol was similar in adult and paediatric patients older than 1 year.

5.2 Pharmacokinetic properties

a) General: Mean absolute bioavailability after intramuscular administration was found to be 100%. Distribution following intravenous administration is rapid and in two phases with half-lives of 0.31 ± 0.17 hours (initial rapid phase) and 1.7 ± 0.4 hours (slower phase). After intravenous administration of 100 mg tramadol, serum concentration was 613 ± 221 ng/ml at 15 minutes 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, mainly by N- and O-demethylation and conjugation of the O-demethylation products with glucuronic acid. Only O-desmethyltramadol is pharmacologically active; eleven metabolites have been found in urine. Animal experiments show O-desmethyltramadol is more potent than the parent substance by a factor of 2–4, with a half-life t½β of 7.9 h (range 5.4–9.6 h), approximately that of tramadol.

Inhibition of one or both of CYP3A4 and CYP2D6, involved in the metabolism of tramadol, may affect plasma concentrations of tramadol or its active metabolite. Tramadol is essentially excreted via the kidneys; mean elimination half-life following intravenous administration is 5–6 hours, and total clearance was 28.0 L/h following intravenous administration.

b) Characteristics in patients: Pharmacokinetics show little age-dependence in volunteers up to 75 years; in volunteers over 75, terminal elimination half-life was 7.0 ± 1.6 h compared to 6.0 ± 1.5 h in young volunteers after oral administration. As tramadol and O-desmethyl tramadol are eliminated both metabolically and renally, terminal half-life may be prolonged in hepatic or renal dysfunction, though the increase is relatively small if either excretory organ is functioning normally. In liver cirrhosis patients, mean t½ of tramadol was 13.3 ± 4.9 hours; in renal failure (creatinine clearance <5 mL/min), t½ of tramadol was 11.0 ± 3.2 hours and of M1 was 16.9 ± 3.0 hours. Extreme values observed were 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: Pharmacokinetics of tramadol and O-desmethyltramadol after single- and multiple-dose oral administration to subjects aged 1–16 years were generally similar to adults when adjusted for body weight, with higher between-subject variability in children 8 years and below. In children below 1

year, pharmacokinetics have been investigated but not fully characterized; the formation rate of O-desmethyltramadol via CYP2D6 increases continuously in neonates, with adult levels of CYP2D6 activity assumed to be reached at about 1 year. Immature glucuronidation systems and 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 occurred only 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 reactions.

In rats, tramadol dosages from 50 mg/kg/day upwards caused toxic effects in dams and raised neonate mortality; retardation occurred in the offspring as ossification disorders and delayed vaginal and eye opening. Male fertility was not affected; at higher doses females exhibited a reduced pregnancy rate. In rabbits, toxic effects in dams occurred from 125 mg/kg upwards, with skeletal anomalies in the offspring.

Some in-vitro test systems showed evidence of mutagenic effects, but in-vivo studies showed no such effects; tramadol can be classified as non-mutagenic. Tumorigenicity studies in rats showed no evidence of substance-related increase in tumour incidence; in mice, an increased incidence of liver cell adenomas in males (dose-dependent, non-significant, from 15 mg/kg upwards) and an increase in pulmonary tumours in females of all dosage groups (significant, but not dose-dependent) were observed.

6. Pharmaceutical particulars

6.1 List of excipients

Benzyl Alcohol, Di Sodium E.D.T.A, Sodium Acetate Trihydrate, Sodium Metabi Sulphite, Tri Sodium Citrate Dihydrate, Citric Acid Anhydrous, Water for Injection.

6.2 Incompatibilities

None stated.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store at a temperature below 30°C, protect from light and moisture.

6.5 Nature and contents of container

Pack size: 10x10x2. Primary packing – 2 ml: 10 x 2 ml clear colour USP Type-1 glass ampoules loaded on a plastic tray; 10 x 2 ml tray loaded clear colour USP Type-1 glass ampoules in an inner printed carton; 10 x 10 x 2 ml clear colour USP Type-1 glass ampoules in an outer printed carton. Finished product.

6.6 Special precautions for disposal and other handling

None.

7. Marketing authorisation holder

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8. Marketing authorisation number(s)

H2024/CTD10655/24271

9. Date of first authorisation/renewal of the authorisation

2024 July 31

10. Date of revision of the text

2024 July 31