Tramadol Hydrochloride Injection

VARDOL® 50 / 100

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

DESCRIPTION
Tramadol hydrochloride is a centrally acting synthetic analgesic in an extended-release formulation. The chemical name is (±) cis-2-[(dimethyl amino) methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. The molecular formula of tramadol hydrochloride is $C_{16}H_{25}NO_2.HCl$ and its molecular weight is 299.8g/mol.

THERAPEUTIC INDICATIONS
Treatment of moderate to severe pain.

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 post-operative severe pain).
Unless otherwise prescribed, Tramadol should be administered as follows:
Adults and adolescents above the age of 12 years: The usual dosage is 50 or 100mg 4-6 hourly. 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 50-100mg 4-6 hourly up to a total daily dose of 400mg.
Older 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 patient's prolongation of the dosage intervals should be carefully considered according to the patient's requirements.
Paediatric population (Children above the age of 1 year): The recommended single dose of tramadol hydrochloride is 1mg/kg to 2mg/kg body weight. The total daily dose of 8mg tramadol hydrochloride per kg body weight or 400mg tramadol hydrochloride, whichever is lower, should not be exceeded per day. On account of their high dosage strengths, capsules, prolonged release tablets and dispersible tablets are not intended for children below the age of 12 years.

Method of administration
The solution for injection is to be injected slowly or diluted in infusion solution and infused. It can be administered by intramuscular, intravenous, subcutaneous injection or intravenous infusion.
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.
Don't use if any particle, leakage or breakage found.

CONTRAINDICATIONS
- Hypersensitivity to the Tramadol Hydrochloride.
- Acute intoxication with alcohol, hypnotics, analgesics, opioids, or other psychotropic medicinal products.
- Patients who are receiving Monoamine oxidase inhibitors or who have taken them within the last 14 days.
- Patients with epilepsy not adequately controlled by treatment.
- For use in narcotic withdrawal treatment.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
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.
Tramadol may only be used with particular caution in opioid-dependent patients, patients with head injury, shock, a reduced level of consciousness of uncertain origin, disorders of the respiratory center 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 (Interaction with Other Medicinal Products and Other Forms of Interactions), or if the recommended dosage is significantly exceeded as the possibility of respiratory depression cannot be excluded in these situations.
Sleep related breathing disorders: Opioids can cause sleep-related breathing disorders including central sleep apnea (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.
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 Interaction with other medicinal products and other forms of interactions, Undesirable effects and Overdose). 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.
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). Tramadol may increase the seizure risk in patients taking other medicinal products that lowers the seizure threshold (Interaction with Other Medicinal Products and Other Forms of Interactions). 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.
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.
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.
Risk from concomitant use of sedative medicines such as benzodiazepines or related medicinal products: Concomitant use of tramadol and sedative medicines such as benzodiazepines or related medicinal products 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 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 (Interaction with Other Medicinal Products and Other Forms of Interactions).

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS
MAO inhibitors: Tramadol should not be used in combination with MAO inhibitors (See Contraindications).
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 tramadol.
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 Tramadol with other centrally depressant medicinal products including alcohol may potentiate the CNS effects (See Undesirable Effects).
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, 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, 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 ºC 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.
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.
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.
Warfarin: Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (e.g. warfarin) due to reports of increased INR, major bleeding and ecchymoses in some patients.
PREGNANCY, LACTATION AND FERTILITY
Pregnancy: Animal studies with tramadol at very high doses have revealed 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. Prolonged use during pregnancy may lead to neonatal withdrawal symptoms.
Lactation: 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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Even when taken according to instructions, tramadol 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, particularly alcohol. Do not drive until you know how the medicine affects you.

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.

System organ class	Undesirable Effects
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.
Metabolism and nutrition disorders	
Rare	Changes in appetite.
Not known	Hypoglycemia.
Psychiatric disorders	
Rare	Hallucinations, confusion, sleep disturbance, delirium, anxiety 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 in cognitive and sensorial capacity (e.g. decision behavior, 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, paraesthesia, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalization, 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, 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

OVERDOSE
Symptoms: In principle, on intoxication with tramadol symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include in particular miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest. Serotonin syndrome has also been reported.
Treatment: The general emergency measures 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. Tramadol is minimally eliminated from the serum by haemodialysis or haemo-filtration. Therefore, treatment of acute intoxication with Tramadol with haemodialysis or haemo filtration alone is not suitable for detoxification.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Opioid analgesic.
ATC code: N02AX02
Mechanism of action: Tramadol is a centrally acting opioid analgesic. It is a non-selective pure agonist at μ, δ and κ opioid receptors with a higher affinity 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 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 Posology and method of administration).

Pharmacokinetic properties
After intramuscular administration in humans, tramadol is absorbed rapidly and completely: the mean peak serum concentration (Cmax) is reached after 45 minutes, and bioavailability is almost 100%.
The half-life of the terminal elimination phase (t½, ß) is 6.0 ± 1.5 h in young volunteers. Tramadol pharmacokinetics show little age-dependence, the minimal changes being therapeutically irrelevant. In patients above the age of 65 years the t½, ß was 6.5 ± 1.7 h on oral administration. Since tramadol is eliminated both metabolically and renally, the terminal half-life t½, ß may be prolonged in impaired hepatic or renal function.
However, the increase in the t½, ß values is relatively low if at least one of these organs is functioning normally. In patients with liver cirrhosis t½, ß Tramadol was a mean of 13.3 ± 4.9 h, in patients with renal insufficiency (creatinine clearance < 5 ml/min) it was 11.0 ± 3.2 h.
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. Up to now, clinically relevant interactions have not been reported.
Tramadol 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 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 human's tramadol is mainly metabolised by means of N- and O-demethylation and conjugation of the O-demethylation products with glucuronic acid. Only Odesmethyltramadol is pharmacologically active. There are considerable inter individual quantitative differences between the other metabolites. So far, 11metabolites have been found in the urine. Animal experiments have shown that Odesmethyltramadol is more potent than the parent substance by the factor 2 - 4. Its half-life, t (6 healthy volunteers) is 7.9 h (range 5.4 – 9.6 h) and is approximately that of tramadol
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 Odesmethyltramadol 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 1year of age.

STORAGE: Store below 30°C.Protect from light. Do not freeze.
Keep out of reach of children.
Don't use Tramadol Hydrochloride Injection after the expiry date printed on label and carton.

PRESENTATION: VARDOL 50/100
Primary Packing: 1 ml (VARDOL 50) & 2ml (VARDOL 100) glass ampoule USP Type- I.
Secondary Packing: Such 10 Ampoule are placed in PVC Tray along with Package insert in mono carton.

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