Prescribing Information

For the use of Registered Medical Practitioner, Hospital or a Laboratory Only.

ZYROTRAM

Tramadol Hydrochloride Injection

COMPOSITION:
Each mL contains:
Tramadol Hydrochloride BP 50 mg.

DESCRIPTION:
Zyrotram (Tramadol Hydrochloride Injection 50 mg/mL), 1 ml ampoules is a clear, colourless liquid filled in 1mL Flint ampoule with Black OPC & 1 Black ring.
Zyrotram (Tramadol Hydrochloride Injection 50 mg/mL), 2 ml ampoules is a clear, colourless liquid filled in 2 mL Flint ampoule with Red OPC & 1 Red ring.
Description of product after dilution: Clear and free from particles

PHARMACOLOGICAL PROPERTIES:
Pharmacodynamic properties:
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.
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 - and O-demethylation and conjugation of the O-demethylation products with glucuronic acid. Only O-desmethyltramadol is pharmacologically active. There are considerable interindividual quantitative differences between the other metabolites. So far, eleven metabolites have been found in the urine. Animal experiments have shown that O-desmethyltramadol is more potent than the parent substance by the factor 2-4. Its half life $t_{½}\beta$ (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.

INDICATIONS:
ZYROTRAM Injection is indicated for the treatment of moderate to severe pain.

DOSAGE AND ADMINISTRATION:
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, ZYROTRAM should be administered as follows:
Adults and adolescents above the age of 12 years:
Tramadol HCl injection is not approved for use in patients below the age of 12 years.
The usual dose is 50 or 100 mg 4-6 hourly.
Intravenous injections must be given slowly over 2-3 minutes.
For post-operative pain administer an initial bolus of 100 mg. During the 60 minutes following the initial bolus, further doses of 50 mg may be given every 10-20 minutes, up to a total dose of 250 mg including the initial bolus. Subsequent doses should be 50mg -100mg 46 hourly up to a total daily dose of 400 mg.
Paediatric population
The safety and efficacy of ZYROTRAM has not been studied in the paediatric population. Therefore, use of ZYROTRAM is not recommended in patients under 12 years of age.
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
ZYROTRAM Injection administered intramuscularly, or diluted in solution (water for injections, sodium chloride solution for injection 0.9% and glucose solution for injection 5%) for administration by infusion or patient controlled analgesia.
Duration of administration
Tramadol hydrochloride injection should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with Tramadol hydrochloride injection 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.
Route of Administration
Intravenous and Intramuscular Route.

CONTRA-INDICATIONS:
ZYROTRAM Injection is contraindicated:
- In patients who have previously shown hypersensitivity to the active substance.
- 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.
- In patients with epilepsy not adequately controlled by treatment.
- For use in narcotic withdrawal treatment.
- Children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids.
- Adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of serious breathing problems.

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SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
ZYROTRAM Injection 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 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. Patients with epilepsy or those susceptible to seizures should only be treated with Tramadol if there are compelling circumstances.
Tolerance, psychological and physical dependence may develop, especially after long-term use. 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.
ZYROTRAM Injection is not a suitable substitute in opioid dependent patients. Although it is an opioid agonist, Tramadol cannot suppress morphine withdrawal symptoms.
When a patient no longer requires therapy with Tramadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.
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.
Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs
Concomitant use of Zyrotram Injection 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.
Paediatric population
The safety and efficacy of ZYROTRAM has not been studied in the paediatric population. Therefore, use of ZYROTRAM is not recommended in patients under 12 years of age.
Respiratory depression
Administer ZYROTRAM cautiously in patients at risk for respiratory depression, including patients with substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression, as in these patients, even therapeutic doses of ZYROTRAM may decrease respiratory drive to the point of apnea. In these patients, alternative non-opioid analgesics should be considered. When large doses of tramadol are administered with anaesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures.
Cytochromes P450 (CYP) 2D6 Ultra-Rapid Metabolism
Some individuals may be CYP2D6 ultra-rapid metabolisers. These individuals convert tramadol more rapidly than other people into its more potent opioid metabolites O-desmethyltramadol (M1). This rapid conversion could result in higher than expected opioid-like side effects including life-threatening respiratory depression. The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese, Japanese and Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16-28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups.

DRUG INTERACTIONS:
Tramadol hydrochloride 50 mg/ml solution for injection or infusion should not be combined with MAO inhibitors.
In patients treated with MAO inhibitors in the 14 days prior to the use of the opioid pethidine, life-threatening interactions on the central nervous system, respiratory and cardiovascular function have been observed. The same interactions with MAO inhibitors cannot be ruled out during treatment with Tramadol 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, 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.
Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (e.g. warfarin) due to reports of increased INR with major bleeding and ecchymoses in some patients.
Other active substances known to inhibit CYP3A4, such as ketoconazole and erythromycin, might inhibit the metabolism of tramadol (N-demethylation) probably also the metabolism of the active O-demethylated metabolite. The clinical importance of such an interaction has not been studied.
In a limited number of studies, the pre- or postoperative application of the antiemetic 5-HT3 antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain.
The administration of Tramadol hydrochloride injection with other centrally depressant medicinal products, including alcohol, may potentiate the CNS effects.

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.

FERTILITY, PREGNANCY AND LACTATION:

Pregnancy

Tramadol has been shown to cross the placenta. There are no adequate and well controlled studies in pregnant women. Safe use in pregnancy has not been established. ZYROTRAM is not recommended for pregnant women.
Tramadol - administered before or during birth - does not affect uterine contractility. In neonates it may induce changes in the respiratory rate which are usually not clinically relevant. Chronic use during pregnancy may lead to neonatal withdrawal symptoms.

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

SIDE 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.

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
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.

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: 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.

Psychiatric disorders:

Rare: hallucinations, confusion, sleep disturbance, delirium, anxiety and nightmares. Psychological adverse reactions may occur following administration of Tramadol hydrochloride injection 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).

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:

Common: fatigue

SYMPTOMS AND TREATMENT OF 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 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 injection with haemodialysis or haemofiltration alone is not suitable for detoxification.

Incompatibilities:

Precipitation will occur if Tramadol hydrochloride injection is mixed in the same syringe with injections of diazepam, diclofenac sodium, indomethacin, midazolam and piroxicam.

Shelf life:

Unopen Ampoule: 36 Months
Solution for Injection or Infusion: 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 injection 0.9% w/v and glucose injection 5% w/v at given concentrations when stored at 25°C. From a microbiological point of view, the product should be used immediately. If not used-immediately, in-use storage times and conditions prior to use are the responsibility of the user.

STORAGE:

Unopen Ampoule: Store below 30°C, protected from light.
Solution for Injection or Infusion: 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 injection 0.9% w/v and glucose injection 5% w/v at given concentrations when stored at 25°C. From a microbiological point of view, the product should be used immediately. If not used-immediately, in-use storage times and conditions prior to use are the responsibility of the user.

PRESENTATION:

ZYROTRAM (Tramadol Hydrochloride Injection 50 mg/mL) available in 1mL and 2mL Ampoule. 5 or 10 ampoules are placed together on U type Plastic ampoule tray each tray is packed in carton with package insert.

Date of Revision: 16/09/2025

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