XTRAM

Ampoules

Composition

Xtram Ampoules

Each 2ml Ampoule contains Tramadol HCl 100 mg (50mg/ml)

Action

Tramadol is a centrally acting analgesic. It is a non-selective pure agonist at mu, delta and kappa opioid receptors with a higher affinity for the mu receptor. Other mechanisms, which may contribute to its analgesic effect, are inhibition of neuronal reuptake of noradrenalin 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 (one tenth) to 1/6 (one sixth) that of morphine.

Pediatric population

Effects of enteral and parenteral administration of Tramadol have been investigated in clinical trials involving more than 2000 pediatric 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 pediatric patients older than 1 year .

Pharmacokinetics

More than 90% of Tramadol is absorbed after oral administration. The mean absolute bioavailability is approximately 70 %, irrespective of the concomitant intake of food. The difference between absorbed and non-metabolized available Tramadol is probably due to the low first-pass effect. The first-pass effect after oral administration is a maximum of 30 %.

Tramadol has a high tissue affinity ($V_{d,ß}$= 203 $\pm$ 40 l). It has a plasma protein binding of about 20 %.
Following a single oral dose administration of Tramadol 100 mg as capsules or tablets to young healthy volunteers, plasma concentrations were detectable within approximately 15 to 45 minutes within a mean C_{max} of 280 to 208 mcg/L and T_{max} of 1.6 to 2h.

Tramadol 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).

Elimination half-life $t_{1/2,ß}$ 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 humans Tramadol is mainly metabolized by means of N- and O-demethylation and conjugation of the O-demethylation products with glucuronic acid. Only O-desmethyltramadol is pharmacologically active. There are considerable interindividual quantitative differences between the other metabolites. So far, eleven metabolites have been found in the urine.

Animal experiments have shown that O-desmethyltramadol is more potent than the parent substance by the factor 2 - 4. Its half-life $t_{1/2,ß}$ (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 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. In cases of impaired hepatic and renal function the half-life may be slightly prolonged. In patients with cirrhosis of the liver, elimination half-lives of 13.3 $\pm$ 4.9 h (tramadol) and 18.5 $\pm$ 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 $\pm$ 3.2 h and 16.9 $\pm$ 3 h, in an extreme case 19.5 h and 43.2 h respectively.

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.

Pediatric 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.

Indications
Xtram Ampoule is indicated for the treatment and prevention of moderate to severe pain..

Contraindications
Tramadol is contraindicated in:
- Individuals with known hypersensitivity to Tramadol or any excipients
- Acute intoxication with alcohol, hypnotics, analgesics, opioids or psychotropic drugs
- Patients who are taking MAO inhibitors or who have taken them within the last 14 days
- Known hypersensitivity to opioids
- Patients with uncontrolled epilepsy or epilepsy not adequately controlled by treatment.

Tramadol must not be used for narcotic withdrawal treatment.

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

The frequencies are defined as follows:
Very common: ≥1/10
Common: ≥1/100, <1/10
Uncommon: ≥1/1000, <1/100
Rare: ≥1/10 000, <1/1000
Very rare: <1/10 000
Not known: cannot be estimated from the available data

Cardiovascular system disorders:
Uncommon: cardiovascular regulation (palpitation, tachycardia, postural hypotension or cardiovascular collapse). These adverse effects may occur especially after intravenous administration and in patients who are physically stressed.
Rare: bradycardia, increase in blood pressure.

Nervous system disorders:
Very common: dizziness.
Common: headache, somnolence.
Rare: changes in appetite, paraesthesia, tremor, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope, speech disorders.
Epileptiform 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. Psychic side effects may occur following administration of Tramadol, which vary individually in intensity and nature (depending on personality and duration of medication). These include changes in mood (usually elation, occasionally dysphoria), changes in activity (usually suppression, occasionally increase) and changes in cognitive and sensorial ability (e.g. decision behavior, perception disorders). Dependence may occur.

Eye disorders:
Rare; blurred vision, miosis, mydriasis.

Respiratory system 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: vomiting, constipation, dry mouth.
Uncommon: retching, gastrointestinal irritation (a feeling of pressure in the stomach, bloating), diarrhea

Skin and subcutaneous disorders:
Common: sweating.
Uncommon: dermal reactions (e.g. pruritus, rash, urticaria).

Musculo-skeletal system disorders:
Rare: muscle weakness.

Hepatobiliary system disorders:
In a few isolated cases, increases in liver enzyme values have been reported in a temporal connection with the therapeutic use of Tramadol.

Renal and urinary system disorders:
Rare: micturition disorders (difficulty in passing urine, dysuria and urinary retention)

General disorders:
Common: fatigue.

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

Metabolism and nutrition disorders:
Not known: hypoglycaemia

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, personalisation, derealisation, paranoia).

Warnings and Precautions

At therapeutic doses, Tramadol has the potential to cause withdrawal symptoms. Rarely, cases of dependence and abuse have been reported.

At therapeutic doses withdrawal symptoms have been reported at a frequency of 1 in 8,000. Reports of dependence and abuse have been less frequent. Because of this potential the clinical need for continued analgesic treatment should be reviewed regularly.

Tramadol has a low dependence potential. On long term use tolerance, psychic and physical dependence may develop. In patients with a tendency to drug abuse or dependence, treatment should be for short periods and under strict medical supervision.

Tramadol Injection is not a suitable substitute in opioid dependent patients. The product does not suppress morphine withdrawal symptoms although it is an opioid agonist.

Tramadol Injection may cause drowsiness and this effect may be potentiated by alcohol and other CNS depressants. Ambulant patients should be warned not to drive or operate machinery if affected.

Tramadol Injection should be used with caution in opioid-dependent patients, patients with head injury, a reduced level of consciousness of uncertain origin, disorders of the respiratory centre or function, increased intracranial pressure, severe impairment of hepatic and renal function and in patients prone to convulsive disorders or in shock. In patients sensitive to opiates the product should only be used with caution.

Convulsions have been reported at therapeutic doses and the risk may be increased at doses exceeding the usual upper daily dose limit (400mg). Patients with a history of epilepsy or those susceptible to seizures should only be treated with Tramadol if there are compelling reasons.

The risk of convulsions may increase in patients taking Tramadol and concomitant medication that can lower the seizure threshold.

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. At therapeutic doses respiratory depression has infrequently been reported.

In one study using a nitrous oxide/opioid (Tramadol) anesthetic technique (with only intermittent administration of enflurane 'as required') Tramadol was reported to enhance intra- operative recall. Hence its use during potentially very light planes of general anesthesia should be avoided.

Two studies of Tramadol administration during anesthesia comprising continuous administration of isoflurane have shown clinically significant lightening of anesthetic depth or intra-operative recall. Therefore providing the current practice of administering continuous, potent (volatile or intravenous) anesthetic agent is followed, Tramadol may be used intra- operatively in the same way as other analgesic agents are routinely used.

This medicinal product contains approximately 8.29mg sodium acetate trihydrate (1.4mg sodium) per 2ml dose.

Pregnancy
Category C
Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Labour and Delivery
Tramadol should not be used in pregnant women prior to or during labour unless the potential benefits outweigh the potential risks, because safe use in pregnancy has not been established. Chronic use during pregnancy may lead to neonatal withdrawal symptoms. If Tramadol were to be used during labour, it may cause respiratory depression in the newborn. Tramadol has been shown to cross the placenta. The mean ratio of serum Tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women given Tramadol during labour.
The effect of Tramadol, if any, on the later growth, development, and functional maturation of the child is unknown.

Use in lactation
Tramadol is not recommended during breast-feeding, because its safety in infants and newborns has not been studied. Low levels of Tramadol have been detected in breast milk. Following a single intravenous 100 mg dose of Tramadol, the cumulative excretion in breast milk within 16 hours post-dose was 100 µg of Tramadol (0.1% of the maternal dose) and 27 µg of M1.

Drug Interactions
Tramadol Injection 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 Injection.

Concomitant administration of Tramadol Injection with other centrally acting drugs, including alcohol, may potentiate CNS depressant 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, tetrahydrocannabinol) to cause convulsions.

Theoretically there is a possibility that Tramadol could interact with lithium. There have been no reports of this potential interaction.

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.

There have been isolated reports of interaction with coumarin anticoagulants resulting in an increased INR with major bleeding and ecchymoses in some patients and so care should be taken when commencing treatment with Tramadol in patients on anticoagulants.

Pharmacokinetic studies were conducted to investigate the effects of cimetidine, quinidine and carbamazepine on the pharmacokinetics of Tramadol.

Carbamazepine – The simultaneous administration of carbamazepine markedly decreases serum concentrations of tramadol to an extent that a decrease in analgesic effectiveness and a shorter duration of action may occur.

Cimetidine - With the concomitant or previous administration of cimetidine clinically relevant interactions are unlikely to occur. Therefore no alteration of the tramadol dosage regimen is recommended for patients receiving chronic cimetidine therapy.

Quinidine - A study in 12 healthy volunteers has shown that quinidine causes an approximate 25% increase in the Tramadol C_{max} and AUC; T_{max} is unaffected. However, the increases in C_{max} and AUC fall within the normal therapeutic range for Tramadol, and no dosage adjustment is required.

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.

Dosage and Administration

Tramadol Injection should not be administered for longer than absolutely necessary. If long-term pain treatment with Tramadol 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.

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 400mg Tramadol hydrochloride should not be exceeded, except in special clinical circumstances.

The Tramadol injection either intramuscularly, by slow intravenous injection or diluted in solution for administration by infusion or patient controlled analgesia.

Adults and children 12 years and over:
The usual dose is 50mg or 100mg 4 to 6 hourly by either intramuscular or intravenous routes. Intravenous injections must be given slowly over 2–3 minutes. The dose should be adjusted according to the severity of the pain and the response.

For post-operative pain, an initial bolus of 100mg is administered. During the 60 minutes following the initial bolus, further doses of 50mg may be given every 10-20 minutes, up to a total dose of 250mg including the initial bolus. Subsequent doses should be 50mg or 100mg 4- 6 hourly up to a total daily dose of 400mg.

Geriatric patients
A dose adjustment is not usually necessary in 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 impairment

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.

Children under 12 years:
Not recommended.

Over Dosage

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 haemofiltration. Therefore treatment of acute Tramadol intoxication with haemodialysis or haemofiltration alone is not suitable for detoxification.

Presentation

Xtram Ampoules
Box of 5 Ampoules