120x170mm

Capsule/Injection

Tramax

(Tramadol hydrochloride)

ٹرامیکس کیپسول/انجیکشن

(ٹرامادول ہائیڈروکلورائیڈ)

COMPOSITION

Tramax capsule 50mg

Each capsule contains:

Tramadol hydrochloride……..50mg

(BP specification)

Tramax injection 100mg

Each 2ml ampoule contains:

Tramadol hydrochloride ……100mg

(BP specification)

INDICATIONS

For the treatment and prevention of moderate to severe pain.

MECHANISM OF ACTION:

Tramadol, a cyclohexanol derivative, 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 also 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.

DOSAGE & 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 400mg tramadol hydrochloride should not be exceeded, except in special clinical circumstances.

Injection

Tramadol should not 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 regular monitoring should be carried out (if necessary with breaks in treatment) to establish whether, and to what extent, further treatment is necessary.

The tramadol solution is for parenteral 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.

Capsule

Unless otherwise prescribed Tramadol should be administered as follows:

Adults and adolescents aged 12 years and over:

Acute pain: An initial dose of 100mg is usually necessary. This can be followed by doses of 50 mg or 100 mg at 4- 6 hourly intervals, and duration of therapy should be matched to clinical need.

Pain associated with chronic conditions:

Use an initial dose of 50mg and then titrate dose according to pain severity. The need for continued treatment should be assessed at regular intervals as withdrawal symptoms and dependence have been reported, although rarely.

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:

Tramadol is not suitable for children below the age of 12 years.

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-metabolised 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,β = 203 ± 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 $t_{1/2}$, β 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 metabolised by means of N- and O-demethylation and conjugation of the O-demethylation products with glucuronic acid. Only O-desmethyltramadol is pharmacologically active. There are considerable interindividual quantitative differences between the other metabolites. So far, 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 t1/2,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.

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 ± 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.

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.

WARNINGS

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.

Tolerance, psychic and physical dependence may develop, especially after long-term use. 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 should be for short periods and under strict medical supervision.

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

Concomitant use of Tramadol Solution for Injection and sedating medicinal substances such as benzodiazepines or related substances, may result in respiratory depression, sedation, coma and death. Concomitant prescribing with these sedating medicinal products should be only undertaken where no other option is available. If concomitant prescribing is the only option, the lowest effective dose of Tramadol should be used, and duration of concomitant treatment should be as short as possible. Patients should be monitored closely for signs and symptoms of respiratory depression and sedation. It is recommended to inform patients and their caregivers to be aware of these symptoms.

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.

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 apnea, led to rare, but life threatening adverse events.

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.

PRECAUTIONS

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

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. At therapeutic doses, respiratory depression has infrequently been reported.

Pregnancy

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 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. Chronic use

120x170mm

during pregnancy may lead to neonatal withdrawal symptoms.
Breast-feeding
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.
DRUG INTERACTIONS
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. Concomitant administration of Tramadol with other centrally depressant medicinal products including alcohol may potentiate the CNS effects.
The concomitant use of opioids with sedating medicinal products such as benzodiazepines or related substances increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose of Tramadol and the duration of the concomitant use should be limited.
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 product (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 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.
SIDE EFFECTS:
Blood and lymphatic system disorders
There have also been cases of blood dyscrasias observed with tramadol treatment, but direct causality has not been confirmed.
Immune system disorders
Rare: hypersensitivity/allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic edema) and anaphylaxis.
Psychiatric disorders:
Rare: sleep disturbance, delirium, anxiety, confusion, nightmares and hallucinations, have been reported. 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 behaviour, perception disorders). Dependence may occur.
Dependence: Prolonged administration of tramadol may lead to dependence.
Withdrawal reactions: 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).
Nervous system disorders:
Very common: dizziness
Common: headache and drowsiness (somnolence)
Rare: changes in appetite, paraesthesia, tremor, respiratory depression, involuntary muscle contractions, abnormal coordination. Epileptiform convulsions have been reported occurring mainly after administration of high doses of tramadol or after treatment with drugs which can lower the seizure threshold or themselves induce cerebral convulsions (e.g. anti-depressants or anti-psychotics), syncope. If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly, respiratory depression may occur.
Not known: speech disorders
Eye disorders:
Rare: blurred vision, mydriasis, blurred vision
Cardiac disorders:
Uncommon: cardiovascular regulation (palpitations, tachycardia). These adverse reactions may occur especially on intravenous administration and in patients who are physically stressed.
Rare: bradycardia, hypertension (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.
Respiratory, thoracic and mediastinal disorders:
Rare: respiratory depression, dyspnea
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 and dry mouth.
Uncommon: retching; gastrointestinal discomfort (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)
Metabolism and nutrition disorders:
Not known: hypoglycemia
General disorders and administration site conditions:
Common: fatigue
CONTRAINDICATIONS
- Tramadol should not be administered to patients who have previously demonstrated hypersensitivity to it, or to any of the ingredients, or in cases of acute intoxication with alcohol, hypnotics, analgesics, opioids or other psychotropic medicinal drugs.
- In common with other opioid analgesics it should not be administered to patients who are receiving monoamine oxidase (MAO) inhibitors or within two weeks of their withdrawal
- Tramadol should not be given to patients suffering from uncontrolled epilepsy.
- Tramadol must not be used for narcotic withdrawal treatment.

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, sedation and consciousness disorders up to coma, seizures 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 intoxication with Tramadol with haemodialysis or haemofiltration alone is not suitable for detoxification.
STORAGE & INSTRUCTIONS:
Store between 15-25°C.
Protect from heat, sunlight and moisture.
Keep away from the reach of children.
To be sold on the prescription of a registered medical practitioner only.
HOW SUPPLIED
Tramax capsule 50mg
10 capsules.
Tramax injection 100mg
1's, 5's, 10's ampoules.

خوراک وطریقہ استعمال:
ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:
دوا کو ۱۵-۲۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔
دھوپ، گرمی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

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