

ZYTRAM[®] XL

Tramadol hydrochloride 150mg, 200mg, 300mg, 400mg modified-release tablets

Presentation

ZYTRAM[®] XL 150mg tablets – White, film coated oval shaped tablets, marked 'TOD 150' on one side, the other side plain.

ZYTRAM[®] XL 200mg tablets – White, film coated oval shaped tablets, marked 'TOD 200' on one side, the other side plain.

ZYTRAM[®] XL 300mg tablets – White, film coated oval shaped tablets, marked 'TOD 300' on one side, the other side plain.

ZYTRAM[®] XL 400mg tablets – White, film coated oval shaped tablets, marked 'TOD 400' on one side, the other side plain.

Uses

Actions

Tramadol is a centrally acting analgesic. It is a non-selective pure agonist at mu, delta and kappa opioid receptors with a greater affinity for the mu receptor. Other mechanisms that contribute to its analgesic effect are inhibition of neuronal re-uptake of noradrenaline and increased serotonin release.

Tramadol is a centrally acting analgesic. Unlike other centrally acting analgesics eg morphine and codeine, tramadol has a dual mechanism of action at therapeutic doses: it possesses opioid agonist properties and modifies transmission of pain impulses at the spinal level by inhibition of monoamines (noradrenaline and serotonin re-uptake).

Tramadol is a racemic mixture; the (+) enantiomer has a weak affinity for the μ opioid receptors and in inhibiting the re-uptake of serotonin whereas the (-) enantiomer preferentially inhibits the re-uptake of noradrenaline. A recent study has demonstrated the safety of both of the enantiomers and the racemate in patient with severe postoperative pain receiving up to 600mg i.v. per day of each respective substance. The enantiomers act in a complimentary and synergistic fashion to produce analgesia, mainly by inhibiting pain transmission in the spinal cord. Although tramadol has an affinity for opioid receptors, this affinity is 6,000 times weaker than that of morphine.

Tramadol has a major advantage over the other opioid analgesics because it has less effect on respiratory and cardiovascular functions at therapeutic doses. These are particularly useful properties in the treatment of pain in the elderly. Care should be taken not to exceed the maximum dose and tramadol should not normally be used in patients with epilepsy because of its effects on the re-uptake of serotonin.

Tramadol has a low potential to cause physical dependence or abuse, approximately 1 in 6,000.

Pharmacokinetics

Following oral administration of a single dose, tramadol is almost completely absorbed and the absolute bioavailability is approximately 70%. Tramadol is metabolised to O-desmethyltramadol, which has been shown to have analgesic activity in rodents. The elimination half-life of tramadol is around 6 hours, although this is extended to 16 hours following prolonged absorption from the ZYTRAM[®] XL tablet.

Following administration of one ZYTRAM[®] XL tablet 200mg in the fasting state, a mean peak plasma concentration (C_{max}) of 192 ng.ml⁻¹ was attained. This was associated with a median t_{max} of 6 hours (range 4-8 hours). The availability of tramadol from the ZYTRAM[®] XL tablet 200mg was complete when compared with an immediate release tramadol solution 100mg, after dose adjustment.

In the presence of food, the availability and controlled release properties of ZYTRAM[®] XL tablets were maintained, with no evidence of dose dumping.

A single-dose proportionality study has confirmed a linear pharmacokinetic response (in relation to tramadol and O-desmethyltramadol) following administration of the 200mg, 300mg and 400mg tablets. A steady state study has confirmed the dose-adjusted bioequivalence of the 150mg and 200mg tablets administered once daily.

The study also confirmed that the ZYTRAM[®] XL tablet 150mg provided an equivalent peak concentration and extent of availability of tramadol to an immediate release capsule 50mg administered 8-hourly. On this basis it is recommended that patients receiving immediate release tramadol should be transferred initially to the nearest daily dose of ZYTRAM[®] XL tablets. It may be necessary to titrate the dose thereafter.

A further steady state study has demonstrated that immediate release tramadol tablets 50mg, administered 6-hourly, provided plasma concentrations that were greater than would have been anticipated following administration of a single dose. This observation is consistent with a non-linear elimination of the drug substance. In contrast, the plasma concentrations from ZYTRAM[®] XL tablet 200mg administered once-daily were in the line with single dose data, confirming that the controlled delivery of tramadol from ZYTRAM[®] XL minimises the non-linearity associated with faster-releasing preparations. The more predictable plasma concentrations may lead to a more manageable dose titration process.

Tramadol and its metabolites are almost completely excreted with the urine.

Indications

Relief of moderate to severe pain.

Dosage and Administration

ZYTRAM[®] XL tablets should be taken at 24-hourly intervals and must be swallowed whole and not chewed.

As with all analgesic medicines, the dose of tramadol should be adjusted according to the severity of the pain and the clinical response of the individual patient. The correct dosage of any individual patient is that which controls the pain with no or tolerable side effects for a full 24 hours. Patients transferring to immediate release tramadol preparations should have their total daily dose calculated, and start on the nearest dose in the ZYTRAM[®] XL range. It is recommended that patients are slowly titrated to higher doses to minimise transient side effects. The need for continued treatment should be assessed at regular intervals as withdrawal symptoms and dependence have been reported (see Section Warnings and Precautions). A total daily dose of 400mg should not be exceeded except in special clinical circumstances.

Adults and children over 12 years

The usual initial dose is one 150mg tablet daily. If pain relief is not achieved, the dosage should be titrated upwards until pain relief is achieved.

Elderly and patients with renal or hepatic impairment

The elimination half-life of tramadol may be prolonged in these patient populations. A starting dose of 150mg daily is recommended. Dose titration upwards should be carefully monitored. Tramadol is not recommended for patients with severe renal impairment (creatinine clearance < 10mL/min).

Children under 12 years

Not recommended.

Contraindications

Hypersensitivity to tramadol; acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs. In common with other opioid analgesics, tramadol should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal.

Warnings and Precautions

Warnings

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.

In patients with a tendency to drug abuse or dependence, treatment should be for short periods and under strict medical supervision.

Tramadol should be used with caution in patients with acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids and psychotropic medicines; receiving MAO inhibitors or who have used them within the last 14 days.

Tramadol is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms.

Precautions

Convulsions have been reported at therapeutic doses and the risk may be increased at doses exceeding the usual upper daily dose limit. 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 (see Section: Interaction).

Tramadol should be used with caution in patients with head injury, increased intracranial pressure, and severe impairment of hepatic and renal functions and in patients prone to convulsive disorders or in shock.

Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered, as the possibility of respiratory depression cannot be excluded in these situations.

In one study using nitrous oxide/opioid (tramadol) anaesthetic technique with only intermittent administration of isoflurane did not show clinically significant lightening of anaesthetic depth or intra-operative recall. Therefore providing the current practice of administering continuous, potent (volatile or intravenous) anaesthetic agent is followed, tramadol may be used intra-operatively in the same way as other analgesic agents are routinely used.

Use in pregnancy

Animal studies (rat and rabbit, exposure to tramadol up to 7 times that expected in man) have not revealed teratogenic effects and showed minimal embryotoxicity (delayed ossification). Fertility, reproductive performance and development of offspring were unaffected. There is inadequate evidence available on the safety of tramadol in human pregnancy; therefore tramadol should not be used in pregnant women.

Use in lactation

Tramadol and its metabolites are found in small amounts in human breast milk. An infant could ingest about 0.1% of the dose given to the mother. Tramadol should not be administered during breast-feeding.

Use in children

The use of Tramadol in children is not recommended as safety and efficacy in children has not been established.

Effect on ability to drive or operate machinery

Due to its sedative effect, patients should be advised to avoid driving or operating heavy machinery while taking tramadol.

Adverse Effects

The following table lists ADRs seen after application of tramadol products including frequency figures where available through authoritative sources.

Body as a Whole <i>Uncommon</i>	Allergic reactions Anaphylaxis
Cardiovascular <i>Uncommon</i>	Hypotension Tachycardia Very rarely Bradycardia Very rarely Hypertension
Gastrointestinal <i>Common</i>	Nausea Vomiting Mouth Dry Constipation GI disorders NOS
Hepato-biliary <i>Uncommon</i>	Hepatic enzymes increased

<p>Central Nervous System <i>Common</i></p> <p><i>Uncommon</i></p>	<p>Dizziness Somnolence</p> <p>Headache Vision Abnormal Emotional Lability, Euphoria Hypoactivity, Hyperactivity Cognitive Disorders, Sensory Disturbance Convulsions Confusion Drug Dependence Hallucinations Withdrawal symptoms which may include: Agitation Anxiety Nervousness Insomnia Hyperkinesia Tremor Gastrointestinal symptoms</p>
<p>Dermatologic <i>Common</i></p> <p><i>Uncommon</i></p>	<p>Sweating</p> <p>Pruritus Rash Urticaria Angioneurotic oedema</p>
<p>Genito-urinary trace <i>Uncommon</i></p>	<p>Micturition disorder Urinary retention</p>
<p>Respiratory tract <i>Uncommon</i></p>	<p>Dyspnoea Bronchospasm Respiratory depression</p>

Interactions

Central nervous system depressants

Tramadol should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anaesthetic agents, phenothiazines, tranquillisers or sedative hypnotics.

The combination of tramadol with mixed opiate agonists/antagonists (eg. buprenorphine, pentazocine) is not advisable because the analgesic effect of a pure agonist may be theoretically reduced in such circumstances.

Tramadol can induce convulsions and increase the potential for selective serotonin reuptake inhibitors, tricyclic antidepressants, antipsychotics and other seizure threshold lowering drugs to cause convulsions.

Co-administration with selective serotonin reuptake inhibitors may lead to an increase in serotonergic effects (serotonin syndrome).

Monoamine oxidase inhibitors

Tramadol should not be used in patients who are taking MAOIs or who have taken them within the last fourteen days, as tramadol inhibits the uptake of noradrenaline and serotonin (see Contraindications).

Coumarin anticoagulants

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

Others

Tramadol does not appear to induce its own metabolism in humans, since observed maximal plasma concentrations after multiple oral doses are higher than expected based on single dose data. Tramadol is a mild inducer of selected drug metabolism pathways measured in animals.

Concomitant administration of tramadol with carbamazepine causes a significant increase in tramadol metabolism, presumably through metabolic induction by carbamazepine. Patients receiving chronic carbamazepine doses of up to 800mg daily may require up to twice the recommended dose of tramadol. Tramadol is metabolised to M1 by the CYP2D6 P450 isoenzyme. Drugs that selectively inhibit that isoenzyme (quinidine, phenothiazines, and antipsychotic agents) may cause increased concentrations of tramadol and decreased concentrations of M1. The clinical consequences of these potential effects have not been fully investigated.

Concomitant administration of tramadol with cimetidine does not result in clinically significant changes in tramadol pharmacokinetics. Therefore no alteration of the tramadol dosage regimen is recommended.

Other medicines known to inhibit the CYP3A4 isoenzyme of cytochrome P450, such as ketoconazole and erythromycin, may inhibit the metabolism of tramadol (via N-demethylation) and probably the metabolism of the active O-demethylated metabolite (M1). The clinical importance of such an interaction has not been studied.

Overdosage

Symptoms of overdosage are typical of other opioid analgesics, and include miosis, vomiting, cardiovascular collapse, sedation and coma, seizures and respiratory depression which may – in severe cases – result in a fatal outcome.

Supportive measures such as maintaining the patency of the airway and maintaining cardiovascular function should be instituted; naloxone should be used to reverse respiratory depression; fits can be controlled with diazepam.

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.

Emptying the gastric contents is useful to remove any unabsorbed drug, particularly when a prolonged release formulation has been taken.

Pharmaceutical Precautions

Store at or below 30°C. Keep out of reach of children.

Medicine Classification

Prescription only medicine.

Package Quantities

150mg, 200mg, 300mg and 400mg tablets: 30 tablets packed in blisters.

Further Information

Active ingredient of the ZYTRAM[®] XL tablets is tramadol hydrochloride.

Inactive ingredients are: Hydrogenated vegetable oil BP, Talc Ph Eur, Magnesium stearate Ph Eur, Lactose Ph Eur, Hypromellose (E464), Titanium dioxide (E171), Macrogol 4000 Ph Eur.

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