

XTRAM PLUS

Tablets

Composition

Xtram plus Tablet

Each Tablet contains Tramadol HCl 37.5 mg & Paracetamol 325mg

Action

Tramadol is a centrally acting synthetic opioid analgesic. Although its mode of action is not completely understood, from animal tests, at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ -opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.

Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ -opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ -opioid binding. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound.

Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin in vitro, as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of tramadol.

Apart from analgesia, tramadol administration may produce a constellation of symptoms (including dizziness, somnolence, nausea, constipation, sweating, and pruritus) similar to that of other opioids.

Paracetamol is a non-opiate, non-salicylate analgesic.

Pharmacokinetics

Absorption

Racemic tramadol is rapidly and almost completely absorbed after oral administration. The mean absolute bioavailability of a single 100 mg dose is approximately 75 %. After repeated administration, the bioavailability is increased and reaches approximately 90 %.

After administration, the oral absorption of paracetamol is rapid and nearly complete and takes place mainly in the small intestine. Peak plasma concentrations of paracetamol are reached in one hour and are not modified by concomitant administration of tramadol.

The oral administration with food has no significant effect on the peak plasma concentration or extent of absorption of either tramadol or paracetamol so that it can be taken independently of meal times.

Distribution

Tramadol has a high tissue affinity ($V_{d,\beta}=203 \pm 40$ l). It has a plasma protein binding of about 20%. Paracetamol appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 l/kg. A relative small portion (~20%) of paracetamol is bound to plasma proteins.

Metabolism

Tramadol is extensively metabolized after oral administration. About 30 % of the dose is excreted in urine as unchanged drug, whereas 60% of the dose is excreted as metabolites.

Tramadol is metabolised through O-demethylation (catalyzed by the enzyme CYP2D6) to the metabolite M1, and through N-demethylation (catalyzed by CYP3A) to the metabolite M2. M1 is further metabolised through N-demethylation and by conjugation with glucuronic acid. The plasma elimination half-life of M1 is 7 hours. The metabolite M1 has analgesic properties and is more potent

than the parent drug. The plasma concentrations of M1 are several-fold lower than those of tramadol and the contribution to the clinical effect are unlikely to change on multiple dosing.

Paracetamol is principally metabolized in the liver through two major hepatic routes: glucuronidation and sulphation. The latter route can be rapidly saturated at doses above the therapeutic doses. A small fraction (less than 4%) is metabolized by cytochrome P 450 to an active intermediate (the N-acetyl benzoquinoneimine) which, under normal conditions of use, is rapidly detoxified by reduced glutathione and excreted in urine after conjugation to cysteine and mercapturic acid. However, during massive overdose, the quantity of this metabolite is increased.

Elimination

Tramadol and its metabolites are eliminated mainly by the kidneys. The half-life of paracetamol is approximately 2 to 3 hours in adults. It is shorter in children and slightly longer in the newborn and in cirrhotic patients. Paracetamol is mainly eliminated by dose-dependent formation of glucuro- and sulpho-conjugate derivatives. Less than 9 % of paracetamol is excreted unchanged in urine. In renal insufficiency, the half-life of both compounds is prolonged.

Gender: The pharmacokinetics of Tramadol is similar in males and females.

Elderly: In the elderly (age over 75 years), the volume of distribution of Tramadol is decreased by 25% and clearance is decreased by 40%. As a result, Tramadol Cmax and total exposure are increased by 30% and 50%, respectively, but the half-life of Tramadol is only slightly prolonged (by 15%).

Hepatic & Renal Insufficiency

Renal

The pharmacokinetics in patients with renal impairment has not been studied. Based on studies using tramadol alone, excretion of tramadol and metabolite M1 is reduced in patients with creatinine clearance of less than 30 mL/min. Adjustment of dosing regimen in this patient population is recommended. The total amount of tramadol and M1 removed during a 4-hour dialysis period is less than 7% of the administered dose based on studies using tramadol alone.

Hepatic

The pharmacokinetics and tolerability in patients with impaired hepatic function have not been studied. Since tramadol and Paracetamol are both extensively metabolized by the liver, the use of in patients with hepatic impairment is not recommended.

Indications

Xtram plus® indicated for the symptomatic treatment of moderate to severe pain.

Contraindications

- Hypersensitivity to tramadol, paracetamol or to any of the excipients of the medicinal product.
- Acute intoxication with alcohol, hypnotic drugs, centrally-acting analgesics, opioids or psychotropic drugs.
- Should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal.
- Severe hepatic impairment.
- Epilepsy not controlled by treatment.

Adverse Reactions

The most commonly reported undesirable effects during the clinical trials performed with the paracetamol/tramadol combination were nausea, dizziness and somnolence, observed in more than 10 % of the patients.

Cardiovascular system disorders:

- Uncommon ($\geq 1/1000$ to $< 1/100$): hypertension, palpitations, tachycardia, arrhythmia.

Central and peripheral nervous system disorders:

- Very common ($\geq 1/10$): dizziness, somnolence
- Common ($\geq 1/100$ to $< 1/10$): headache trembling
- Uncommon ($\geq 1/1000$ to $< 1/100$): involuntary muscular contractions, paraesthesia, tinnitus
- Rare ($\geq 1/10000$ to $< 1/1000$): ataxia, convulsions, syncope.

Psychiatric disorders:

- Common ($\geq 1/100$ to $< 1/10$): confusion, mood changes (anxiety, nervousness, euphoria), sleep disorders
- Uncommon ($\geq 1/1000$ to $< 1/100$): depression, hallucinations, nightmares, amnesia
- Rare ($\geq 1/10000$ to $< 1/1000$): drug dependence.

Post marketing surveillance

Very rare ($< 1/10000$): abuse.

Vision disorders:

- Rare ($\geq 1/10000$ to $< 1/1000$): blurred vision

Respiratory system disorders:

- Uncommon ($\geq 1/1000$ to $< 1/100$): dyspnoea

Gastro-intestinal disorders:

- Very common ($\geq 1/10$): nausea
- Common ($\geq 1/100$ to $< 1/10$): vomiting, constipation, dry mouth, diarrhoea abdominal pain, dyspepsia, flatulence
- Uncommon ($\geq 1/1000$ to $< 1/100$): dysphagia, melaena.

Liver and biliary system disorders:

- Uncommon ($\geq 1/1000$ to $< 1/100$): hepatic transaminases increase.

Skin and appendages disorders:

- Common ($\geq 1/100$ to $< 1/10$): sweating, pruritus
- Uncommon ($\geq 1/1000$ to $< 1/100$): dermal reactions (e.g. rash, urticaria).

Urinary system disorders:

- Uncommon ($\geq 1/1000$ to $< 1/100$): albuminuria, micturition disorders (dysuria and urinary retention).

Body as a whole:

- Uncommon ($\geq 1/1000$ to $< 1/100$): shivers, hot flushes, thoracic pain.

Metabolism and nutrition disorders:

- Unknown: hypoglycaemia

Drug abuse and dependence

Abuse

Tramadol has mu-opioid agonist activity, a tramadol-containing product, can be abused and may be subject to criminal diversion.

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. Drug addiction is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, use for non-medical purposes, continued use despite harm or risk of harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.

“Drug-seeking” behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated “loss” of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse can occur in the absence of true addiction and is

characterized by misuse for non-medical purposes, often in combination with other psychoactive substances.

Concerns about abuse and addiction should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Proper assessment of the patient and periodic re-evaluation of therapy are appropriate measures that help to limit the potential abuse of this product.

Dependence

Tolerance is the need for increasing doses of drugs to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Generally, tolerance and/or withdrawal are more likely to occur the longer a patient is on continuous therapy.

Warnings and Precautions

Warnings

In adults and adolescents 12 years and older, the maximum dose of 8 tablets of Xtram plus should not be exceeded. In order to avoid inadvertent overdose, patients should be advised not to exceed the recommended dose and not to use any other paracetamol (including over the counter) or tramadol hydrochloride containing products concurrently without the advice of a physician.

In severe renal insufficiency (creatinine clearance <10 ml/mm), Xtram plus is not recommended.

In patients with severe hepatic impairment Xtram plus should not be used. The hazards of paracetamol overdose are greater in patients with non-cirrhotic alcoholic liver disease. In moderate cases prolongation of dosage interval should be carefully considered.

In severe respiratory insufficiency, Xtram plus is not recommended.

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

Convulsions have been reported in tramadol-treated patients susceptible to seizures or taking other medications that lower the seizure threshold, especially selective serotonin re-uptake inhibitors, tricyclic antidepressants, antipsychotics, centrally acting analgesics or local anaesthesia. Epileptic patients controlled by a treatment or patients susceptible to seizures should be treated with Xtram plus only if there are compelling circumstances. 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 dose limit

Concomitant use of opioid agonists-antagonists (nalbuphine, buprenorphine, pentazocine) is not recommended.

Precautions

Tolerance and physical and/or psychological dependence may develop, even at therapeutic doses. The clinical need for analgesic treatment should be reviewed regularly. In opioid-dependent patients and patients with a history of drug abuse or dependence, treatment should only be for short period

and under medical supervision. Xtram plus should be used with caution in patients with cranial trauma, in patients prone to convulsive disorder, biliary tract disorders, in a state of shock, in an altered state of consciousness for unknown reasons, with problems affecting the respiratory center or the respiratory function, or with an increased intracranial pressure.

Paracetamol in overdosage may cause hepatic toxicity in some patients.

Symptoms of withdrawal reaction, similar to those occurring during opiate withdrawal, may occur even at therapeutic doses and for short term treatment. Withdrawal symptoms may be avoided by tapering it at the time of discontinuation especially after long treatment periods. Rarely, cases of dependence and abuse have been reported).

Symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal may occur.

In one study, use of tramadol during general anaesthesia with enflurane and nitrous oxide was reported to enhance intra-operative recall. Until further information is available, use of tramadol during light planes of anaesthesia should be avoided.

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

Xtram plus should not be used in pregnant women prior to or during labor unless the potential benefits outweigh the risks. Safe use in pregnancy has not been established. Chronic use during pregnancy may lead to physical dependence and post-partum withdrawal symptoms 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 labor.

The effect of Xtram plus, if any, on the later growth, development, and functional maturation of the child is unknown.

Use in lactation

Since Xtram plus is a fixed combination of active ingredients including tramadol, it should not be ingested during breast feeding.

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding by women using single ingredient medicinal products containing only paracetamol.

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 ingested during breast feeding.

Drug Interactions

CYP2D6 and CYP3A4 Inhibitors

Concomitant administration of CYP2D6 and/or CYP3A4 inhibitors, such as quinidine, fluoxetine, paroxetine and amitriptyline (CYP2D6 inhibitors), and ketoconazole and erythromycin (CYP3A4 inhibitors), may reduce metabolic clearance of tramadol, increasing the risk for serious adverse events including seizures and serotonin syndrome.

Serotonergic Drugs

There have been post marketing reports of serotonin syndrome with use of tramadol and SSRIs/SNRIs or MAOIs and α 2-adrenergic blockers. Caution is advised when coadministration with other drugs that may affect the serotonergic neurotransmitter systems, such as SSRIs, MAOIs, triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, or St. John's Wort. If concomitant

treatment with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Triptans

Based on the mechanism of action of tramadol and the potential for serotonin syndrome, caution is advised with coadministration with a triptan. If concomitant treatment with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Use with Carbamazepine

Patients taking carbamazepine may have a significantly reduced analgesic effect of tramadol. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration with carbamazepine is not recommended.

Use with Quinidine

Tramadol is metabolized to M1 by CYP2D6. Quinidine is a selective inhibitor of that isoenzyme; so that concomitant administration of quinidine and tramadol results in increased concentrations of tramadol and reduced concentrations of M1. The clinical consequences of these findings are unknown. In vitro drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism.

Potential for Other Drugs to Affect Tramadol

In vitro drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and amitriptyline could result in some inhibition of the metabolism of tramadol. Administration of CYP3A4 inhibitors, such as ketoconazole and erythromycin, or inducers, such as rifampin and St. John's Wort may affect the metabolism of tramadol, leading to altered tramadol exposure.

Potential for Tramadol to Affect Other Drugs

In vitro studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when tramadol is administered concomitantly at therapeutic doses. 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.

Use with Cimetidine

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

Use with Digoxin

Post-marketing surveillance of tramadol has revealed rare reports of digoxin toxicity.

Use with Warfarin-Like Compounds

Post-marketing surveillance of both tramadol and Paracetamol individual products have revealed rare alterations of warfarin effect, including elevation of prothrombin times.

While such changes have been generally of limited clinical significance for the individual products, periodic evaluation of prothrombin time should be performed when warfarin-like compounds are administered concurrently.

Dosage and Administration

ADULTS AND ADOLESCENTS (12 years and older)

The dose should be individually adjusted according to intensity of pain and response of the patient.

An initial dose of two tablets of Xtram plus® is recommended. Additional doses can be taken as needed, not exceeding 8 tablets (equivalent to 300 mg tramadol and 2600 mg paracetamol) per day.

The dosing interval should not be less than six hours.

Xtram plus® should under no circumstances be administered for longer than is strictly necessary. If repeated use or long term treatment with Xtram plus® is required as a result of the nature and severity of the illness, then careful, regular monitoring should take place (with breaks in the treatment, where possible), to assess whether continuation of the treatment is necessary.

Children

The effective and safe use of Xtram plus® has not been established in children below the age of 12 years. Treatment is therefore not recommended in this population.

Elderly patients

The usual dosages may be used although it should be noted that in volunteers aged over 75 years the elimination half life of tramadol was increased by 17% following oral administration. In patients over 75 years old, it is recommended that the minimum interval between doses should be not less than 6 hours, due to the presence of tramadol.

Renal insufficiency

Because of the presence of tramadol, the use of Xtram plus® is not recommended in patients with severe renal insufficiency (creatinine clearance < 10 ml/min). In cases of moderate renal insufficiency (creatinine clearance between 10 and 30 ml/min), the dosing should be increased to 12-hourly intervals. As tramadol is removed only very slowly by haemodialysis or by haemofiltration, post dialysis administration to maintain analgesia is not usually required.

Hepatic insufficiency

In patients with severe hepatic impairment Xtram plus® should not be used. In moderate cases prolongation of the dosage interval should be carefully considered.

Method of administration

Oral use

Tablets must be swallowed whole, with a sufficient quantity of liquid. They must not be broken or chewed.

Over Dosage

The clinical presentation of overdose may include the signs and symptoms of tramadol toxicity, Paracetamol toxicity or both. The initial symptoms of tramadol overdosage may include respiratory depression and/or seizures. The initial symptoms seen within the first 24 hours following a Paracetamol overdose are: anorexia, nausea, vomiting, malaise, pallor and diaphoresis. An overdosage of may be a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Tramadol

Acute overdosage with tramadol can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, seizures, bradycardia, hypotension, cardiac arrest, and death.

Deaths due to overdose have been reported with abuse and misuse of tramadol. Review of case reports has indicated that the risk of fatal overdose is further increased when tramadol is abused concurrently with alcohol or other CNS depressants, including other opioids.

In the treatment of tramadol overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and

pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

While naloxone will reverse some, but not all, symptoms caused by overdosage with tramadol, the risk of seizures is also increased with naloxone administration. In animals, convulsions following the administration of toxic doses of (Tramadol/Paracetamol) could be suppressed with barbiturates or benzodiazepines but were increased with naloxone. Naloxone administration did not change the lethality of an overdose in mice. Hemodialysis is not expected to be helpful in an overdose because it removes less than 7% of the administered dose in a 4-hour dialysis period.

Paracetamol

In Paracetamol overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and coagulation defects also may occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

In the treatment of Paracetamol overdosage, gastric decontamination with activated charcoal should be administered just prior to N-acetylcysteine (NAC) to decrease systemic absorption if Paracetamol ingestion is known or suspected to have occurred within a few hours of presentation. Serum Paracetamol levels should be obtained immediately if the patient presents 4 or more hours after ingestion to assess potential risk of hepatotoxicity; Paracetamol levels drawn less than 4 hours post-ingestion may be misleading. To obtain the best possible outcome, NAC should be administered as soon as possible where impending or evolving liver injury is suspected. Intravenous NAC may be administered when circumstances preclude oral administration.

Vigorous supportive therapy is required in severe intoxication. Procedures to limit the continuing absorption of the drug must be readily performed since the hepatic injury is dose-dependent and occurs early in the course of intoxication.

Presentation

Xtram plus® Tablets

Box of 20 Tablets