

## XTRAM

Capsules

### Composition

#### Xtram 50 mg capsule

Each capsule contains Tramadol HCl 50 mg

### Action

Tramadol is a centrally acting synthetic analgesic of the aminocyclohexanol group with opioid-like effects. It is not derived from natural sources, nor is it chemically related to opiates. Although pre-clinical testing has not completely explained the mode of action, at least two complementary mechanisms appear applicable: binding to  $\mu$ -opioid receptors and inhibition of re-uptake of noradrenaline and serotonin. The opioid-like activity of Tramadol derives from low affinity binding of the parent compound to  $\mu$ -opioid receptors and higher affinity binding of the principal active metabolite, O-desmethyltramadol, denoted M1, to  $\mu$ -opioid receptors. In animal models, M1 is up to 6 times more potent than Tramadol in producing analgesia and 200 times more potent in  $\mu$ -opioid binding. The contribution to human analgesia of Tramadol relative to M1 is unknown.

Both animal and human studies have shown that antinociception induced by Tramadol is partially antagonized by the opiate antagonist naloxone. In addition, Tramadol shown to inhibit re-uptake of noradrenaline and serotonin in vitro, as have some other opioid analgesics. These latter mechanisms may contribute independently to the overall analgesic profile of Tramadol.

The analgesic effect is dose-dependent, but the relationship between serum concentrations and analgesic effect varies considerably between individuals. In one study, the median serum concentration of Tramadol required for effective post-operative analgesia was 300 ng/mL, with individual values ranging from 20 to 990 ng/mL

Apart from analgesia, Tramadol may produce other symptoms similar to that of opioids including dizziness, somnolence, nausea, constipation, sweating, and pruritus. However, Tramadol causes significantly less respiratory depression than morphine. In contrast to morphine, Tramadol has not been shown to cause histamine release. At therapeutic doses, Tramadol has no clinically significant effect on heart rate, left ventricular function, or cardiac index. Orthostatic changes in blood pressure observed.

### Pharmacokinetics

#### *Absorption*

Tramadol is rapidly and completely absorbed after oral administration of 50 mg capsules following a mean absorption delay ( $t_0$ ) of approximately thirty minutes. The absorption half-life ( $t_{1/2}$ ) is  $23 \pm 11$  minutes.

Oral administration of Tramadol with food does not significantly affect its rate or extent of absorption. Therefore, Tramadol can be administered without regard to food.

After repeated oral administration of 50 mg and 100 mg Tramadol capsules at six hourly intervals, steady state is reached 30 to 36 hours after the first administration and the bioavailability is greater than 90%.

#### *Distribution*

Tramadol is rapidly distributed in the body, with a volume of distribution of 2 - 3 L/kg in young adults. The volume of distribution is reduced by about 25% in those aged over 75 years. Plasma protein binding is about 20% and is independent of concentration up to 10  $\mu$ g/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range.

Tramadol crosses the placental and blood-brain barriers. Very small amounts of Tramadol and M1 are found in breast milk (0.1% and 0.02% respectively of the administered dose).

### *Metabolism*

Tramadol is extensively metabolised after oral administration. The major metabolic pathways appear to be N - and O -demethylation and glucuronidation or sulfation in the liver. Only O -desmethyltramadol (M1) is pharmacologically active. Production of M1 is dependent on the CYP2D6 isoenzyme of cytochrome P450. Patients who metabolize drugs poorly via CYP2D6 may obtain reduced benefit from Tramadol, due to reduced formation of M1. N-demethylation is catalyzed by the CYP3A4 isoenzyme of cytochrome P450. 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.

### *Elimination*

Mainly the kidneys, with a cumulative renal excretion (Tramadol and metabolites) of approximately 95%, excrete Tramadol and its metabolites. In young adults approximately 15 - 19% of an administered dose of Tramadol is excreted in the urine as unmetabolised drug. In the elderly, this increases to about 35%. Biliary excretion is of little importance. In young adults, the half-life of Tramadol is 5 - 7 h and the half-life of M1 is 6 - 8 h. Total clearance is approximately 430 - 610 mL/min.

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 C<sub>max</sub> and total exposure are increased by 30% and 50%, respectively, but the half-life of Tramadol is only slightly prolonged (by 15%).

### *Hepatic Insufficiency & Renal Insufficiency*

Elimination of Tramadol and M1 is impaired in patients with hepatic or renal impairment. In patients with hepatic impairment, the mean half-life of Tramadol was found to be 13 h (range up to 19 h), and the mean half-life of M1 was 19 h (range up to 36 h). In patients with severe renal impairment (creatinine clearance < 5 mL/min) the mean half-life of Tramadol was 11 h (range up to 20 h), and the mean half-life of M1 was 17 h (range up to 43 h).

## **Indications**

Xtram is indicated for the management of moderate to severe, acute, or chronic pain and in painful diagnostic or therapeutic procedures.

## **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**

Adverse reactions that may occur after administration of Tramadol resemble those known to occur with opioids. Adverse reactions recorded in 13,802 patients from trials with different formulations of Tramadol. The nature and incidence of reactions (in CIOMS format where very common  $\geq 1/10$ ; common  $\geq 1/100$  and  $<1/10$ ; uncommon  $\geq 1/1000$  and  $<1/100$ ; rare  $\geq 1/10,000$  and  $<1/1000$ ; were as follows:

### *Cardiovascular*

Uncommon: orthostatic dysregulation (tendency to collapse, and cardiovascular collapse) and tachycardia, flushing

Rare: increase in blood pressure, bradycardia

#### *Respiratory*

Rare: dyspnoea

#### *Gastrointestinal*

Very common: nausea

Common: vomiting, constipation

Uncommon: dyspepsia, diarrhea, abdominal pain, flatulence, urge to vomit

Rare: changes in appetite

#### *Neurological*

Very common: dizziness

Common: autonomic nervous effects (mainly dry mouth, perspiration), headache sedation, asthenia, fatigue.

Uncommon: trembling

Rare: changes in mood (usually elevation, occasionally dysphoria) paraesthesia, hallucinations, confusion, coordination disturbance, sleep disturbance, anxiety, nightmares, motor system weakness, changes in appetite, tremor, respiratory depression, seizures, involuntary muscle contractions, changes in activity (usually suppression, occasionally increase), changes in cognitive and sensorial capacity (eg. decision behavior, perception disorders), syncope

#### *Hypersensitivity and skin*

Common: sweating

Uncommon: skin reactions, pruritus, rash

Rare: shock reactions, anaphylaxis, allergic reactions

#### *Genitourinary*

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

#### *Special senses*

Rare: visual disturbance (blurred vision)

The incidence of "non-specific CNS irritation" (dizziness), "autonomic nervous effects" (perspiration), "orthostatic dysregulation (tendency to collapse and cardiovascular collapse) and tachycardia and "nausea/urge to vomit/vomiting" can be increased with rapid intravenous administration and also tends to be dose dependent. No tests of significance have been performed.

#### *Drug abuse and dependence*

Although Tramadol can produce drug dependence of the  $\mu$ -opioid type (like codeine or dextropropoxyphene) and potentially may be abused, there has been little evidence of abuse in clinical experience to date. In clinical trials, Tramadol produced some effects similar to an opioid, and at supratherapeutic doses was recognized as an opioid in subjective/behavioral studies. Part of the activity of Tramadol is thought to be derived from its active metabolite, which is responsible for some delay in onset of activity and some extension of the duration of  $\mu$ -opioid activity. Delayed  $\mu$ -opioid activity is believed to reduce a drug's abuse liability.

On long term treatment (6 months or more) habituation and dependence cannot be rolled out

#### *Tolerance and withdrawal*

Tolerance development has been reported to be relatively mild. 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.

## **Warnings and Precautions**

### **Acute abdominal conditions**

The administration of Tramadol may complicate the clinical assessment of patients with acute abdominal conditions.

### **Respiratory depression**

Tramadol should be administered cautiously in patients at risk of respiratory depression.

When large doses of Tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Cases of intra-operative respiratory depression, usually with large intravenous doses of Tramadol and with concurrent administration of respiratory depressants, have been reported.

Increased intracranial pressure or head trauma

Tramadol should be used with caution in patients with increased intracranial pressure, head injury, shock, or a reduced level of consciousness of uncertain origin. Pupillary changes (miosis) from Tramadol may obscure the existence, extent, or course of intracranial pathology. Clinicians should also maintain a high index of suspicion for adverse drug reaction when evaluating altered mental status in these patients if they are receiving Tramadol.

### **Renal and hepatic disease**

With the prolonged half-life in these conditions, achievement of steady state is delayed, so that it may take several days for elevated plasma concentrations to develop.

#### **Renal disease**

Impaired renal function results in a decreased rate and extent of excretion of Tramadol and its active metabolite, M1. In patients with creatinine clearances of less than 30 mL/min, dosage reduction is recommended. Tramadol is not recommended in patients with severe renal impairment (creatinine clearance <10 mL/min). As Tramadol is removed very slowly by haemodialysis or haemofiltration, post-dialysis administration to maintain analgesia is not usually necessary.

#### **Hepatic disease**

Metabolism of Tramadol and M1 is reduced in patients with advanced cirrhosis of the liver. In cirrhotic patients, dosage reduction is recommended.

#### **Effects on ability to drive and use machinery**

Due to its sedative effect, patients should be advised to avoid driving or operating machinery whilst taking Tramadol.

#### **Patients physically dependent on opioids**

Tramadol is not recommended as a substitute in opioid-dependent patients. Although Tramadol is an opiate-agonist, it cannot suppress opioid withdrawal symptoms. Animal experiments have shown that under certain circumstances the administration of Tramadol may provoke a withdrawal syndrome in opioid-dependent monkeys. Because of the difficulty in assessing dependence in patients who have previously received substantial amounts of opioid medications, caution should be used in the administration of Tramadol to such patients.

In patients with a tendency for drug abuse or dependence, treatment with Tramadol should only be carried out for short periods under strict medical supervision.

Cases of dependence and abuse of Tramadol have been reported rarely.

#### **Seizure risk**

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. In addition, Tramadol may increase the seizure risk in patients taking other medication that lowers the seizure threshold (see Interactions with other drugs). Patients with epilepsy or those susceptible to seizures should only be treated with Tramadol if there are compelling circumstances.

#### **Anaphylactoid reactions**

Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving Tramadol. These reactions often occur following the first dose. Other reported reactions include pruritus, hives, bronchospasm, and angioedema.

#### **Intra-operative use**

In one study using nitrous oxide/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 levels of general anesthesia should be avoided. Two recent studies of Tramadol administration during anesthesia comprising continuous administration of isoflurane did not show 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.

#### **Long-term use**

Tramadol studied in controlled clinical trials for periods of up to three months. In one small-uncontrolled study, patients with cancer pain received a dose of 150 mg Tramadol per day for up to six months. Beyond six months, no clinical studies investigating the safety and efficacy of Tramadol are available.

When Tramadol treatment of pain is required long-term, careful and regular monitoring should be carried out to establish whether, and to what extent, ongoing treatment is necessary.

#### **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**

*Use with CNS depressants* - Tramadol should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anesthetic agents, phenothiazines, tranquillizers, 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.

*Use with other serotonergic agents* - the presence of another drug that increases serotonin by any mechanism should alert the treating physician to the possibility of an interaction. In isolated cases,

there have been reports of serotonin syndrome in a temporal connection with the therapeutic use of tramadol in combination with other serotonergic medicines such as selective serotonin re-uptake inhibitors (SSRIs). Signs of serotonin syndrome may be, for example, confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus, and diarrhea. Withdrawal of the serotonergic medicines usually brings about a rapid improvement. Drug treatment depends on the nature and severity of the symptoms.

*Use with coumarin derivatives* - caution should be exercised during concomitant treatment with Tramadol and coumarin derivatives (eg. warfarin) due to reports of increased international normalized ratio (INR) with major bleeding and ecchymoses in some patients.

*Drugs that reduce the seizure threshold* - Tramadol can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors, tricyclic antidepressants, antipsychotics and other seizure threshold lowering agents to cause convulsions.

*Use with MAO inhibitors* - Tramadol should not be used in patients who are taking MAO inhibitors or who have taken them within the last fourteen days, as Tramadol inhibits the uptake of noradrenaline and serotonin.

*Other interactions* - 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 800 mg 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 are 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 drugs 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.

In a limited number of studies, the pre- or post-operative application of the antiemetic 5-HT<sub>3</sub> antagonist ondansetron increased the requirement of Tramadol in patients with postoperative pain.

## **Dosage and Administration**

The dose of Tramadol should be titrated to the severity of the pain and the clinical response of the individual patient. Tramadol approved for use in adults, adolescents, and children over the age of 2 years

*Oral administration* - For the treatment of moderate pain XTram, 50 - 100 mg administered two or three times daily may be sufficient. XTram 50 mg may be adequate as the initial dose for moderate pain.

For moderate to severe pain, 50 - 100 mg as needed for relief, every four to six hours may be administered.

Tramadol 100 mg is usually more effective as the initial dose for more severe pain.

The maximum daily dose should not exceed 400 mg per day.

*Uses in the elderly - in subjects over the age of 75 years, serum concentrations are slightly elevated and the elimination half-life is slightly prolonged. Subjects in this age group are also expected to vary more widely in their ability to tolerate adverse drug effects. Daily doses in excess of 300 mg are not recommended in patients over 75 years.*

*Renal insufficiency - impaired renal function results in a decreased rate and extent of excretion of Tramadol and M1. In patients with creatinine clearances of less than 30 mL/min, adjustment of the dosage regimen is recommended. In these patients, the dosage interval of Tramadol should be increased to 12 hours. Since only 7% of an administered dose is removed by haemodialysis, dialysis patients can receive their regular dose on the day of dialysis. Tramadol is not recommended in patients with severe renal impairment (creatinine clearance <10 mL/min.).*

*Hepatic insufficiency - In hepatic impairment, the initial oral dose of Tramadol is 50 mg of the immediate release formulation. Depending on the severity of the impairment and individual clinical response, the recommended dosage interval (4-6 hours) may require to be extended, and/or the dose level titrated as required.*

## **Over Dosage**

Few cases of overdose with Tramadol have been reported.

### *Symptoms*

Symptoms of overdosage with Tramadol are similar to those of other centrally acting analgesics (opioids) and include miosis, vomiting, cardiovascular collapse, consciousness disorders including coma, convulsions, respiratory depression and respiratory arrest.

### *Treatment*

Should overdosage occur, general emergency measures should be implemented? Keep the respiratory airways open, and maintain respiration and circulation. If overdosage is due to ingestion of an oral dose form, emptying the stomach by gastric lavage should be considered because of the possibility of ongoing release in the stomach.

Activated charcoal may reduce absorption of the drug if given within 1-2 hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, considerations should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

Naloxone will reverse respiratory depression, but not all symptoms caused by overdosage with Tramadol. Convulsions occurring in mice following the administration of toxic doses of Tramadol could be suppressed with barbiturates or benzodiazepines, but were increased with naloxone. If convulsions are observed, diazepam should be given intravenously. Naloxone did not change the lethality of an overdose in mice.

Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore, treatment of overdosage with Tramadol with haemodialysis or haemofiltration alone is not suitable for detoxification.

## **Presentation**

**XTram 50 mg capsule**

Box of 10 capsules