

SUMMARY OF PRODUCT CHARACTERISTICS

Tramal[®] retard



1. NAME OF THE MEDICINAL PRODUCT

Tramal[®] retard 100 mg
Tramal[®] retard 150 mg
Tramal[®] retard 200 mg

Active substance: tramadol hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One Tramal[®] retard 100 mg prolonged-release tablet contains 100 mg tramadol hydrochloride.

One Tramal[®] retard 150 mg prolonged-release tablet contains 150 mg tramadol hydrochloride.

One Tramal[®] retard 200 mg prolonged-release tablet contains 200 mg tramadol hydrochloride.

Other components: see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablets

Round, biconvex film-coated tablets with the manufacturer's logo engraved on one side.

100 mg tablet: white tablet, marked T1 on the other side.

150 mg tablet: light-orange tablet, with the sign T2 on the other side.

200 mg tablet: brownish-orange tablet, marked T3 on the other side.

4. CLINICAL PARTICULARS

4.1 Indications

Treatment of moderate to severe pain

4.2 Dosage, Mode and Duration of Administration

The dosage should be adjusted to the intensity of the pain and the sensitivity of the individual patient.

Unless otherwise prescribed, the dosage of Tramal retard is as follows:

Adults and adolescents above the age of 12 years

The usual initial dose is 100 mg twice daily (equivalent to 200 mg tramadol hydrochloride daily), preferably in the morning and evening. If pain relief is inadequate, the dose can be raised to 150 mg or 200 mg twice daily (equivalent to 300-400 mg tramadol hydrochloride daily).

The prolonged-release tablets are to be swallowed whole with adequate amounts of fluid - independent of meals.

In principle, the lowest analgesically effective dose should be selected. Daily doses of 400 mg active substance should not be exceeded, unless especially indicated.

On no account should Tramal retard be taken for longer than absolutely necessary. If long-term pain therapy with Tramal retard appears to be necessary on account of the nature and severity of the disease, checks should be carried out at short, regular intervals (if necessary with breaks in treatment) to determine whether and to what extent further treatment is necessary.

Children

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

Geriatric patients

Dose adjustment is not usually necessary in elderly patients (up to 75 years) with no clinically manifest hepatic or renal insufficiency. In geriatric patients (above 75 years) elimination may be prolonged. Therefore, if necessary, the dosage intervals are to be extended according to the patient's requirements.

Hepatic and renal insufficiency/dialysis

Tramal retard should not be given to patients with severe hepatic and/or renal insufficiency. In less severe cases prolongation of the dosage interval should be considered.

4.3 Contraindications

Tramal retard must not be used in known hypersensitivity towards tramadol or any of the other components (see section 6.1 "Other Components"), acute intoxication with alcohol, hypnotics, analgesics, opioids or psychotropics, or in patients who are receiving MAO inhibitors or have taken them within the last 14 days (see section 4.5 "Interactions with Other Medicinal Products and Other Forms of Interaction").

Tramal retard must not be used in cases of epilepsy that are not adequately managed.

Tramal retard must not be used for narcotic withdrawal treatment.

4.4 Precautions and Warnings

Tramal retard must only be used with special care in cases of opioid dependence, head injury, shock, consciousness disorders of uncertain origin, disorders of the respiratory centre or function, increased cerebral pressure.

In patients sensitive to opiates the medicinal product should only be used with caution.

Convulsions have been reported in patients receiving tramadol in the recommended dosage. The risk may be increased on administration of dosages exceeding the

recommended daily dose (400 mg). On concomitant administration of drugs that lower the convulsion threshold tramadol may increase the risk of convulsions (see section 4.5 "Interactions with Other Medicinal Products and Other Forms of Interaction"). Patients with epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling circumstances.

Tramadol has a low dependence potential. On long-term use tolerance, psychic and physical dependence may develop. In patients with a tendency towards medicine abuse or dependence, treatment with Tramal retard should only be carried out for short periods and under strict medical supervision.

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

This medicine contains 2.5 mg lactose per tablet. Patients with rare hereditary galactose intolerance, Lapp lactase deficiency or glucose/galactose malabsorption should consult their physician before taking the preparation.

4.5 Interactions with Other Medicinal Products and Other Forms of Interaction

Tramal retard must not be combined with MAO inhibitors (see section 4.3 "Contraindications").

On premedication with MAO inhibitors in the last 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 Tramal retard.

Concomitant administration of Tramal retard with other centrally depressant substances, including alcohol, may potentiate the CNS effects (see section 4.8 "Side-effects").

Pharmacokinetic studies have 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 curtail the duration of action.

The combination of mixed agonist/antagonists (e.g. buprenorphine, nalbuphine, pentazocine) and tramadol is not advisable, because the analgesic effect of a pure agonist may theoretically be reduced in such circumstances.

Tramadol may induce convulsions and increase the potential of selective serotonin re-uptake inhibitors, tricyclic antidepressants, neuroleptics and other seizure-threshold-lowering drugs to cause convulsions.

There have been isolated reports of serotonin syndrome in a temporal connection with the therapeutic use of tramadol in combination with other serotonergic substances such as selective serotonin re-uptake inhibitors (SSRI) or MAO inhibitors. Symptoms of serotonin syndrome are, for example, confusion, restlessness, pyrexia, sweating, ataxia, hyperreflexia, myoclonia and diarrhoea. When the serotonergic medicines are withdrawn, there is usually a rapid improvement. Medicinal countermeasures depend on the nature and severity of the symptoms.

On the concomitant administration of tramadol and coumarin derivatives (e.g. warfarin) patients should be carefully monitored, as in some patients reduced prothrombin time values and ecchymosis have been observed.

Other CYP3A4 inhibitors, such as ketoconazole and erythromycin, may inhibit the metabolism of tramadol (N-demethylation) and the active O-demethylated metabolite. The clinical significance of this interaction is not known (see section 4.8 "Side-effects").

4.6 Pregnancy and Lactation

Animal studies have shown that very high doses of tramadol affect organ development, bone growth, and neonate mortality rate. Teratogenic effects have not been observed. Tramadol passes the placental barrier. Sufficient evidence of the safety of tramadol during pregnancy in humans is not available. Therefore Tramal retard should not be administered to pregnant women.

When given before or during delivery, tramadol does not affect uterine contractility. In neonates it may induce changes in the respiratory rate which are usually not clinically relevant. About 0.1% of the tramadol dose given to the mother is excreted in the breast-milk during lactation. Tramal retard should not be given to lactating women. After a single administration of tramadol it is not usually necessary to interrupt breast-feeding.

4.7 Effects on Ability to Drive and Operate Machinery

Even when taken according to instructions, Tramal retard may affect reactions to such an extent that road safety or operating machinery may be affected. This applies particularly in conjunction with psychotropic substances.

4.8 Side-effects

The most common side-effects are nausea and dizziness in more than 10% of patients.

Cardiovascular system

Uncommon (< 1%): effect on cardiovascular regulation (palpitation, tachycardia, orthostatic hypotension or cardiovascular collapse). These adverse effects may occur particularly on intravenous administration and in patients who are physically stressed.

Rare (< 0.1%): bradycardia, hypertension

Central and peripheral nervous system

Very common (> 10%): dizziness

Common (1-10%): headache, muzziness

Rare (< 0.1%): changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform seizures.

If the recommended dosages are considerably exceeded or on the concomitant use of other centrally acting substances (see section 4.5 "Interactions with Other Medicinal Products and Other Forms of Interaction"), respiratory depression may occur.

Epileptiform seizures mainly occurred after high tramadol dosages or on the concomitant use of drugs that may lower the seizure threshold (see sections 4.4 "Precautions and Warnings" and 4.5 "Interactions with Other Medicinal Products and Other Forms of Interaction").

Psychic side-effects

Rare (< 0.1%): hallucinations, confusion, sleep disorders and nightmares.

After administration of Tramal retard a variety of psychic side-effects that vary in intensity and nature from patient to patient (depending on personality and duration of treatment) may occur. These include changes in mood (usually euphoria, occasionally dysphoria), changes in activity (usually depression, occasionally increase), and changes in cognitive and sensory perception (e.g. decision-making, perception disorders).

Dependence may occur.

Visual disorders

Rare (< 0.1%): blurred vision

Respiratory organs

Deterioration of asthma has been reported. However, a causal connection has not been established.

Gastrointestinal tract

Very common (> 10%): nausea

Common (1-10%): vomiting, constipation, dry mouth

Uncommon (< 1%): urge to vomit, gastrointestinal irritation (e.g. feeling of pressure in the stomach, bloating)

Skin and skin appendages

Common (1-10%): sweating

Uncommon (< 1%): dermal reactions (e.g. pruritus, rash, urticaria)

Musculoskeletal system

Rare (< 0.1%): motorial weakness

Liver and biliary tract

In a few isolated cases elevated liver enzyme values have been reported in a temporal connection with the therapeutic use of tramadol.

Urinary tract

Rare (< 0.1%): micturition disorders (difficulties in passing water)

Generalised

Rare (< 0.1%): allergic reactions (e.g. dyspnoea, bronchospasm, rhonchi, angioneurotic oedema) and anaphylaxis

Withdrawal symptoms similar to those of opiates may occur. These symptoms include: agitation, anxiety, nervousness, sleep disorders, hyperkinesia, tremor, and gastrointestinal symptoms. Other symptoms observed in very rare cases after discontinuation of tramadol include: attacks of panic, severe anxiety, hallucinations, paraesthesia, tinnitus, and unusual CNS symptoms.

4.9 Overdose

Symptoms

In principle, on intoxication with tramadol symptoms similar to those of other centrally acting analgesics (opioids) may occur. These include in particular miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Therapy

The general emergency measures apply in keeping open the respiratory tract (aspiration!), maintaining respiration and circulation depending on the symptoms. The stomach is to be emptied by inducing vomiting (conscious patient) or rinsing. An antidote for respiratory depression is naloxone. In animal experiments naloxone had no effect on convulsions. In such cases diazepam should be given intravenously.

Tramadol can only minimally be removed by means of dialysis. Therefore haemodialysis or haemofiltration alone is not suitable for the treatment of acute intoxication with Tramal retard.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

ATC code: N 02 AX 02: analgesics

Tramadol 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 that contribute to its analgesic effect are the inhibition of the neuronal re-uptake of noradrenaline 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. Nor is gastrointestinal motility affected. The cardiovascular effects tend to be slight. The potency of tramadol is reported to be 1/10 to 1/6 that of morphine.

5.2 Pharmacokinetic Properties

More than 90% of Tramal retard is absorbed after oral administration. Absolute bioavailability is a mean of about 70%, irrespective of the concomitant intake of food. The difference between absorbed and non-metabolised tramadol is probably due to the low first-pass effect. After oral administration the first-pass effect is a maximum of 30%.

Tramadol has a high tissue affinity ($V_{d,\beta} = 203 \pm 40$ l). Serum protein binding is about 20%.

After administration of Tramal retard 100 mg the peak plasma concentration C_{\max} after 4.9 h is 141 ± 40 ng/ml. After administration of Tramal retard 200 mg C_{\max} is 260 ± 62 ng/ml after 4.8 h.

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).

The elimination half-life $t_{1/2,\beta}$ is approx. 6 h, irrespective of the mode of administration. In patients above the age of 75 years it may be prolonged by a factor of approx. 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, 11 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 $t_{1/2,\beta}$ (six healthy volunteers) is 7.9 h (range: 5.4 - 9.6 h) and is approximately that of tramadol.

Inhibition of the iso-enzyme CYP3A4 and/or CYP2D6 involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolites. So far no clinically relevant interactions have 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 ± 4.9 h (tramadol) and 18.5 ± 4.9 h (O-desmethyltramadol) have been determined, in an extreme case 22.3 h and 36 h respectively. 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 dose range. The relation 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.

5.3 Preclinical Safety Data

On repeated oral and parenteral administration of tramadol for 6-26 weeks in rats and dogs and oral administration for 12 months in dogs, haematological, clinico-chemical and histological tests showed no evidence of any substance-related changes. Central nervous manifestations only occurred after high doses far above the therapeutic dose: restlessness, salivation, spasms, reduced weight increase. Rats and dogs tolerated oral doses of 20 mg/kg and 10 mg/kg body weight respectively, and dogs rectal doses of 20 mg/kg body weight, without any effects.

In rats tramadol dosages from 50 mg/kg daily upwards had toxic effects in the dams and there was an increase in neonate mortality. In the offspring retardation in the form of ossification disorders and delayed vaginal and eye opening occurred. Male fertility was not affected. After high doses (from 50 mg/kg/day upwards) females exhibited a reduced pregnancy rate. In rabbits there were toxic effects in dams from 125 mg/kg upwards and skeletal anomalies in the offspring.

In some in-vitro test systems there was evidence of mutagenic effects. In-vivo studies showed no such effects. According to knowledge gained so far, tramadol can be classified as non-mutagenic.

Studies on the tumorigenic potential of tramadol hydrochloride have been carried out in rats and mice. The study in rats showed no evidence of any substance-related increase in the incidence of tumours. In the study in mice there was an increased incidence of liver-cell adenomas in male animals (a dose-dependent, non-significant increase from 15 mg/kg upwards) and an increase in pulmonary tumours in females of all dosage groups (significant, but not dose-dependent).

6. PHARMACEUTICAL PARTICULARS

6.1 Other Components

Tramal retard 100 mg

Microcrystalline cellulose, hypromellose, lactose monohydrate, macrogol 6000, magnesium stearate (Ph.Eur.), propylene glycol, colloidal anhydrous silica, talc, titanium dioxide (E 171).

Tramal retard 150 mg

Microcrystalline cellulose, quinoline yellow (E 104), ferric oxide (E 172), hypromellose, lactose monohydrate, macrogol 6000, magnesium stearate (Ph.Eur.), propylene glycol, colloidal anhydrous silica, talc, titanium dioxide (E 171).

Tramal retard 200 mg

Microcrystalline cellulose, quinoline yellow (E 104), ferric oxide (E 172), ferric oxides and hydroxides, hypromellose, lactose monohydrate, macrogol 6000, magnesium stearate (Ph.Eur.), propylene glycol, colloidal anhydrous silica, talc, titanium dioxide (E 171).

6.2 Principal Incompatibilities

Not applicable.

6.3 Shelf-life

5 years

6.4 Special Precautions for Storage

No special requirements.

6.5 Nature and Contents of Container

AL/PP or AL/PVC/PVDC foil

Packs of 10 and 30 prolonged-release tablets

6.6 Instructions for Use and Handling

No special instructions.

7. NAME AND ADDRESS OF THE PHARMACEUTICAL COMPANY

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8. DATE OF REVISION OF THE TEXT

April 2005

9. LEGAL CATEGORY

Prescription-only