

Tramadol[®] 50 Capsules

Active Ingredient: Tramadol HCl 50mg

Description

Snap-fit, green cap and yellow body, hard gelatine capsule (size 3), containing a white odourless powder.

Pharmacodynamics

Tramadol is a centrally acting opioid analgesic, effective for moderate to severe acute and chronic pains. Tramadol consists of two enantiomers. The (+)-isomer is predominantly active as an opiate with a higher affinity for the μ -opiate receptor (20, times higher affinity than the (-)-isomer). The (+)-desmethyl metabolite will certainly contribute to its action as an opiate as well.

The metabolite has a six times stronger affinity for the μ -receptor in vivo than tramadol. In vitro this affinity is 170 times stronger. The (-)-isomer acts as an inhibitor of the re-uptake of noradrenaline and potentiates the analgesic action of the (+)-isomer. The contribution of the stimulation of the serotonin release is considered low. Tramadol has an analgesic and antitussive effect. 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.

Pharmacokinetics

Absorption

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

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

After administration of tramadol 100 mg prolonged-release tablets the peak plasma concentration $C_{\max}$ 141 ± 40 ng/ml is reached after 4.9 hours. After administration of tramadol 200 mg prolonged-release tablets a $C_{\max}$ 260 ± 62 ng/ml is reached after 4.8 hours.

Distribution

Tramadol passes the blood-brain and placental barriers. Very small amounts of tramadol and its O-desmethyl derivative are found in the breast milk (0.1% and 0.02% respectively of the applied dose).

Biotransformation

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 compound by the factor 2-4. Its half-life $t_{1/2, \beta}$ (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.

Elimination

Elimination half-life ($t_{1/2, \beta}$) is approximately 6 hours, irrespective of the mode of administration. In patients above 75 years of age it may be prolonged by a factor of approximately 1.4.

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 case 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.

Linearity

Tramadol has a linear pharmacokinetic profile within the therapeutic dose 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.

Indications

Management of moderate to severe pain.

Recommended Dose

Unless otherwise prescribed, the following dosage guidelines apply:

Tramadol should not in any circumstances be used longer than therapeutically absolutely necessary.

If the nature and severity of the disease makes more prolonged analgesic treatment with tramadol necessary, a regular, careful and frequent check should be carried out (possibly by the use of treatment-free intervals) to determine whether and to what extent a medical requirement still exists.

Tramadol should be adjusted to the severity of pain and the patient's individual sensitivity. For moderately severe pain, tramadol should be given at the following dosage:

Adults and adolescents (12 years and older)

Tramador® 50 is not approved for use in patients below 12 years old.

1-2 capsules **Tramador®** 50, equivalent to 50-100mg tramadol hydrochloride. Single oral dose of tramadol hydrochloride ranging from 50 – 200mg have provided relief of postoperative pain in patients who have undergone various types of surgery.

If a dose of 1 capsule of **Tramador®** 50 is not followed by adequate pain relief within 30-60 minutes, a single second dose of 1 capsule of **Tramador®** 50 may be given.

In severe pain, if clinical experience suggests that a higher analgesic dose is likely to be

required, the initial dose may be 2 capsules **Tramadol**[®] 50.

Not suitable for children weighing less than 25kg and cannot usually be dosed individually for children under 14 years. An oral solution and an injectable solution are available for this purpose.

The duration of action of tramadol hydrochloride is an average of 4-8 hours, depending on the severity of pain, when therapeutic doses are given.

Daily doses of up to 8 capsules of **Tramadol**[®] 50 (400mg tramadol hydrochloride) are generally adequate. In the treatment of tumour-induced pain, however, much higher daily doses may be used. (150 to 400mg daily in divided doses).

The duration of action of tramadol may be prolonged in patients with disorders of renal or hepatic function.

The need for dosage alterations in elderly patients is under discussion. There is some evidence that elderly patients require lower doses of tramadol than younger patients.

Creatinine clearance should be monitored and used as a determining factor for dosage adjustment. Age alone is not sufficient criteria for dosage adjustment.

While the usual oral tramadol hydrochloride dosage of 50-100mg every 4-6 hours as needed can be used in geriatric patients 65 years and older with normal renal and hepatic function, it is recommended that dosage not exceed 300mg daily in those over 75 years of age.

Dosage of tramadol hydrochloride should be reduced in certain patients with renal or hepatic impairment by decreasing the frequency of administration.

Adults and children 16 years of age and older with creatinine less than 30ml/min may receive an oral **Tramadol**[®] 50 dosage of 50- 100 mg every 12 hours, not exceed 200mg daily. Since less than 10% dose tramadol hydrochloride is removed by haemodialysis, patients undergoing dialysis may receive their usual dosage on the day of dialysis.

Adults and children 16 years of age and older with hepatic cirrhosis may receive a **Tramadol**[®] 50 dosage of 50mg every 12 hours.

The capsules should be taken with a fluid, without relation to meal times.

Notes

The recommended dosages are guideline only. In principle, the lowest effective analgesic dose should be chosen. In the treatment of chronic pain, strict time-tabling of doses is preferred.

Paediatric population

The safety and efficacy of **Tramadol**[®] 50 has not been studied in the paediatric population. Therefore, use of **Tramadol**[®] 50 is not recommended in patients under 12 years of age.

Route of Administration

Oral

Contraindication

Tramadol[®] 50 is contraindicated

- in hypersensitivity to tramadol or any of the excipients
- in acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids, or psychotropic medicinal products

- in patients who are receiving monoamine oxidase (MAO) inhibitors or within two weeks of their withdrawal (see **Drug Interactions**)
- in patients with epilepsy not adequately controlled by treatment
- for use in narcotic withdrawal treatment
- in children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids.
- in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnoea or severe lung disease, which may increase the risk of serious breathing problems.

Warnings and Precautions

Tramadol may only be used with particular caution in

- opioid-dependent patients,
- patients with head injury, shock, a reduced level of consciousness of uncertain origin,
- disorders of the respiratory centre or function,
- and increased intracranial pressure.
- renal and hepatic impairment (see **Recommended Dose**).

In patients sensitive to opiates tramadol should only be used with caution.

Respiratory depression

Administer **Tramadol**® 50 cautiously in patients at risk for respiratory depression, including patients with substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression, as in these patients, even therapeutic doses of **Tramadol**® 50 may decrease respiratory drive to the point of apnoea. In these patients, alternative non-opioid analgesics should be considered. When large doses of tramadol are administered with anaesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures.

Sleep-related breathing disorders

Opioids may cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. Opioids may also cause worsening of pre-existing sleep apnoea (see **Side Effects**). In patients who present with CSA, consider decreasing the total opioid dosage.

Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, decreased appetite, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement dosing of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Risks from Concomitant Use with Benzodiazepines

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of **Tramadol**® 50 with benzodiazepines. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve

concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use.

If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response.

If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response.

Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when **Tramadol**[®] 50 is used with benzodiazepines. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of benzodiazepines (See **Drug Interactions**).

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 (400 mg). In addition, tramadol may increase the seizure risk in patients taking other medicinal products that lowers the seizure threshold (see **Drug Interactions**). Patients with epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling circumstances.

Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent use of **Tramadol**[®] 50 with serotonergic drugs (See **Drug Interactions**). This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea) and can be fatal (See **Drug Interactions**). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue **Tramadol**[®] 50 if serotonin syndrome is suspected.

Sexual Function/Reproduction

Long term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (See **Post-Marketing Experience**)

Cytochromes P450 (CYP) 2D6 Ultra-Rapid Metabolism

Some individuals may be CYP2D6 ultra-rapid metabolisers. These individuals convert tramadol more rapidly than other people into its more potent opioid metabolites O-desmethyltramadol (M1). This rapid conversion could result in higher than expected opioid-like side effects including life-threatening respiratory depression. The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5% to 1% in Chinese, Japanese and Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16-28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups.

Paediatric population

The safety and efficacy of **Tramadol**[®] 50 has not been studied in the paediatric population. Therefore, use of **Tramadol**[®] 50 is not recommended in patients under 12 years of age.

Interactions with Other Medicaments

Tramadol must not be combined with monoamine oxidase (MAO) inhibitors (see **Contraindications**)

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 (see **Side Effects**).

Co-administration with cimetidine is associated with a small prolongation of the half-life of tramadol, but this is not clinically relevant.

Simultaneous or previous administration of carbamazepine (enzyme inducer) may reduce the analgesic effect and shorten the duration of action.

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, ritonavir 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 (see **Side Effects**).

Serotonergic Drugs

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 products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue **Tramadol**[®] 50 if serotonin syndrome is suspected. Examples of serotonergic drugs are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT₃ receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) (See **Warnings and Precautions**).

Benzodiazepines

Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.

The concomitant use of opioids and benzodiazepines increases the risk of respiratory

depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ -receptors, and benzodiazepines interact at GABAA sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see **Warnings and Precautions**).

Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

Pregnancy and Lactation

Pregnancy

Animal studies with tramadol revealed at very high doses effects on organ development, ossification and neonatal mortality. Teratogenic effects have not been observed.

Tramadol has been shown to cross the placenta. There are no adequate and well-controlled studies in pregnant women. Safe use in pregnancy has not been established. **Tramadol[®] 50** Cis not recommended for pregnant women.

Tramadol administered before or during birth does not affect uterine contractility. In neonates it may induce changes in respiratory rate which are not usually clinically relevant.

Lactation

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 400mg, 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.

Side Effects

The most commonly reported adverse reactions are nausea and dizziness, both occurring in more than 10 % of patients.

The frequencies are defined as follows:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$)

Not known (cannot be estimated from the available data)

Immune system disorders

Rare: Allergic reactions (e.g., dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis

Metabolism and nutrition disorders

Rare: Changes in appetite

Not known: Hypoglycaemia

Psychiatric disorders

Rare: hallucination, confusion, delirium, anxiety, sleep disturbances and nightmares
Psychic adverse reactions may occur following administration of tramadol hydrochloride, which vary individually in intensity and nature (depending on personality and duration of treatment). These include changes in mood (usually euphoric mood, 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.

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, paraesthesia, tinnitus and unusual CNS symptoms (i.e., confusion, delusions, personalisation, derealisation, paranoia).

Nervous system disorders

Very common: Dizziness

Common: Headache, somnolence

Rare: Speech disorders, paraesthesia, tremor, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope

Not known: Sleep apnoea syndrome, Serotonin syndrome

Convulsions occurred mainly after administration of high doses of tramadol or after concomitant treatment with medicinal products which can lower the seizure threshold (see **Warning and Precautions and Drug Interactions**).

Eye disorders

Rare: Blurred vision, mydriasis, miosis

Cardiac disorders

Uncommon: Cardiovascular regulation (palpitation, tachycardia). These adverse reactions may occur especially on intravenous administration and in patients who are physically stressed.

Rare: Bradycardia

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, dyspnoea

Not known: Hiccups

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, dry mouth

Uncommon: retching, gastrointestinal discomfort (a feeling of pressure in the stomach, bloating), diarrhoea

Hepatobiliary disorders

Very rare: In a few isolated cases an increase in liver enzyme values has been reported in a temporal connection with the therapeutic use of tramadol.

Skin and subcutaneous tissue disorders

Common: Hyperhidrosis

Uncommon: dermal reactions (e.g. Pruritus, rash, urticarial)

Musculoskeletal and connective tissue disorders

Rare: Motorial weakness

Renal and urinary disorders

Rare: Micturition disorders (dysuria and urinary retention)

General disorders and administration site conditions

Common: Fatigue

Investigation

Rare: Increase in blood pressure

Post-Marketing Experience:

Serotonin syndrome (See **Warnings and Precautions**)

Adrenal insufficiency (See **Warnings and Precautions**)

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids. Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

Infertility: Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

Symptoms and Treatment of 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, consciousness disorders up to coma, convulsions 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 or prolonged-release formulations.

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.
Serotonin syndrome has also been reported.

Effects on Ability to Drive and Use Machine

Even when taken according to instructions, tramadol may cause effects such as somnolence and dizziness and therefore may impair the reactions of drivers and machine operators. This applies particularly in conjunction with other psychotropic substances, particularly alcohol.

Storage Condition

Store in a cool dry place at 30 °C.
Protect from light.
Keep out of reach of children.
Jauhi daripada kanak-kanak

Shelf life:

Please refer to outer carton

List of Excipients

Magnesium stearate
Sodium starch glycollate
Calcium hydrogen phosphate, dehydrate

Packing

Box of 5 x 10 capsules & 10 x 10 capsules

Revision date:

February 2026

Keep out of reach of children.

Contract Manufactured By:

Salutas Pharma GmbH
Otto-von-Guericke-Allee 1,
D-39179 Barleben, Germany.
(a subsidiary of Hexal AG)

For:

HEXAL AG
Holzkirchen. Germany.