

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tramadol 50mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50mg tramadol hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard

White hard gelatine capsules for oral administration, printed with ID Mark 'TR50'

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Management (treatment and prevention) of moderate to severe pain.

4.2 Posology and method of administration

Posology

Treatment should be short and intermittent as dependence can occur with tramadol. The benefits of continued use should be reviewed in order to ensure that they outweigh the risks of dependence (see Special warnings & Special precautions for use and Undesirable effects section).

As with all analgesic drugs, the dose of Tramadol 50mg Capsules should be adjusted according to the severity of the pain and the clinical response of the individual patient. The lowest effective dose for analgesia should generally be selected.

Geriatric patients

A dose adjustment is not usually necessary in patients up to 75 years without clinically manifest hepatic or renal insufficiency. In elderly patients over 75 years' elimination may be prolonged. Therefore, if necessary the dosage interval is to be extended according to the patient's requirements.

Renal insufficiency/dialysis and hepatic impairment

In patients with renal and/or hepatic insufficiency the elimination of tramadol is delayed. In these patient's prolongation of the dosage intervals should be carefully considered according to the patient's requirements.

Adults and children aged 12 years and over: Oral administration.

Acute Pain:

An initial dose of 100mg is usually necessary. This can then be followed by doses of 50mg or 100mg not more frequently than 4 hourly, and duration of therapy should be matched to clinical need.

Pain associated with chronic conditions:

Use an initial dose of 50mg and then titrate dose accordingly to pain severity. The need for continued treatment should be assessed at regular intervals as withdrawals symptoms and dependence have been reported (see section 4.4).

The lowest analgesically effective dose should generally be selected. Daily doses of 400mg active substance should not be exceeded, except in special clinical circumstances.

The capsules should be swallowed whole, not divided or chewed, with sufficient liquid and independently of meals.

Tramadol should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with Tramadol is necessary in view of the nature and severity of the illness, then careful and regular monitoring should be carried out (if necessary with breaks in treatment) to establish whether and to what extent further treatment is necessary.

Elderly

No adjustment of dosage is necessary in elderly patients up to 75 years, as there is no significant difference in tramadol pharmacokinetics with increasing age. However, it should be noted that in volunteers aged over 75 years, the elimination half-life of tramadol was increased by 17% following oral administration. Therefore, if necessary, the dosage interval is to be extended according to the patient's requirements.

Renal Impairment / renal dialysis

The elimination of tramadol may be prolonged, hence in these patient's prolongation of dosage intervals should be carefully considered according to the patients requirements. It is recommended that the usual initial dosage be used and when repeated dosing is required the interval between doses is extended. For patients with creatinine clearance < 30ml/min, the dosage interval should be increased to 12 hours. Tramadol is not recommended for patients with severe renal impairment (creatinine clearance < 10ml/min).

As tramadol is only removed very slowly by haemodialysis or haemofiltration, postdialysis administration to maintain analgesia is not usually necessary.

Hepatic impairment

The elimination of tramadol may be prolonged. The usual initial dosage should be used but in severe hepatic impairment the dosage interval should be increased to 12 hours.

Children aged 12 years and under:

On account of their high dosage strength, Tramadol 50mg Capsules are not recommended for use in children under 12 years of age.

4.3 Contraindications

Tramadol is contraindicated

- in hypersensitivity to tramadol or to any of the excipients listed in section 6.1,
- in acute intoxication with alcohol, hypnotics, analgesics, opioids, or psychotropic medicinal products,
- in patients who are receiving MAO inhibitors or who have taken them within the last 14 days (see section 4.5),
- in patients with epilepsy not adequately controlled by treatment,
- for use in narcotic withdrawal treatment.

4.4 Special warnings and precautions for use

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, increased intracranial pressure.

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

Concomitant use of Tramadol and sedating medicinal products such as benzodiazepines or related substances, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedating medicinal products should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Tramadol concomitantly with sedating medicinal products, the lowest effective dose of Tramadol should be used, and the duration of the concomitant treatment should be as short as possible. The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered (see section 4.5), or if the recommended dosage is significantly exceeded (see section 4.9) as the possibility of respiratory depression cannot be excluded in these situations.

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 section 4.5).

Patients with epilepsy or those susceptible to seizures should be only treated with tramadol if there are compelling circumstances.

Tolerance, psychic and physical dependence may develop especially after long-term use. In patients with a tendency to drug abuse or dependence, treatment with Tramadol should only be carried out for short periods under strict medical supervision.

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

When a patient no longer requires therapy with tramadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

CYP2D6 metabolism:

Tramadol is metabolised by the liver enzyme CYP2D6. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect may not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an ultra-rapid metaboliser there is a risk of developing side effects of opioid toxicity even at commonly prescribed doses.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life threatening and very rarely fatal.

Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised below:

Population	Prevalence
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6 to 6.5%
Greek	6.0 %
Hungarian	1.9%
Northern European	1% to 2%

Post-operative use in children:

There have been reports in the published literature that tramadol given postoperatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events. Extreme caution should be exercised when tramadol is administered to children for post-operative pain relief and should be accompanied by close monitoring for symptoms of opioid toxicity including respiratory depression.

Children with compromised respiratory function:

Tramadol is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of opioid toxicity.

4.5 Interaction with other medicinal products and other forms of interactions

Tramadol should not be combined with MAO inhibitors (see section 4.3).

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 section 4.8).

The concomitant use of opioids (e.g. Codeine, morphine, pentazocine, nalbuphine and buprenorphine) with sedating medicinal products such as benzodiazepines or related substances increase the risk of sedation, respiratory depression, coma and death

because of additive CNS depressant effect. The dose of Tramadol and the duration of the concomitant use should be limited (see section 4.4)

The results of pharmacokinetic studies have so far 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 shorten the duration of action.

Tramadol can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic anti-depressants, anti-psychotics (e.g. Lithium) and other seizure threshold-lowering medicinal products (such as bupropion, Mirtazapine, tetrahydrocannabinol) to cause convulsions.

Concomitant therapeutic use of Tramadol and serotonergic drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see section 4.3), tricyclic antidepressants and Mirtazapine may cause serotonin toxicity. Serotonin syndrome is likely when one of the following is observed:

- Spontaneous clonus
- Inducible or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature > 38°C and inducible or ocular clonus.

Withdrawal of the serotonergic medicinal products usually brings about a rapid improvement. Treatment depends on the nature and severity of the symptoms.

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 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 section 4.8).

In a limited number of studies, the pre- or postoperative application of the antiemetic 5-HT3 antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies with tramadol revealed at very high doses effects on organ development, ossification and neonatal mortality. Tramadol crosses the placenta. There is inadequate evidence available on the safety of tramadol in human pregnancy. Therefore Tramadol should not be used in pregnant women.

Tramadol - administered before or during birth - does not affect uterine contractility. In neonates it may induce changes in the respiratory rate which are usually not clinically relevant. Chronic use during pregnancy may lead to neonatal withdrawal symptoms.

Breast-feeding

During lactation about 0.1 % of the maternal dose is secreted into the milk. TRAMADOL is not recommended during breast-feeding. After a single administration of tramadol it is not usually necessary to interrupt breastfeeding.

Fertility

Post marketing surveillance does not suggest an effect of Tramadol on fertility. Animal studies did not show an effect of Tramadol on fertility.

4.7 Effects on ability to drive and use machines

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 alcohol and other psychotropic substances.

4.8 Undesirable 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: ≥1/10

Common: ≥1/100, <1/10

Uncommon: ≥1/1000, <1/100

Rare: ≥1/10 000, <1/1000

Very rare: <1/10 000

Not known: cannot be estimated from the available data.

Cardiovascular 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.

Investigations:

Rare: Increase in blood pressure

Nervous system disorders:

Very common: dizziness

Common: headache, somnolence

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

Convulsions occurred mainly after administration of high doses of tramadol or after concomitant treatment with medicinal products which can lower the seizure threshold (see sections 4.4 and 4.5).

Respiratory, thoracic and mediastinal disorders:

Rare: respiratory depression, dyspnoea

If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly (see section 4.5), respiratory depression may occur. Worsening of asthma has been reported, though a causal relationship has not been established.

Psychiatric disorders:

Rare: hallucinations, confusion, sleep disturbance, delirium, anxiety and nightmares. Psychic adverse reactions may occur following administration of Tramadol which vary individually in intensity and nature (depending on personality and duration of treatment). These include changes in mood (usually elation, occasionally dysphoria), changes in activity (usually suppression, occasionally increase) and changes in cognitive and sensorial capacity (e.g. decision behaviour, perception disorders). Drug 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, depersonalisation, derealisation, paranoia).

Eye disorders:

Rare: miosis, mydriasis, blurred vision

Gastrointestinal disorders:

Very common: nausea

Common: vomiting, constipation, dry mouth

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

Skin and subcutaneous disorders:

Common: hyperhidrosis

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

Musculoskeletal and connective tissue disorders:

Rare: motorial weakness

Hepatobiliary disorders:

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

Renal and urinary disorders:

Rare: micturition disorders (dysuria and urinary retention)

Metabolism and nutrition disorders:

Rare: changes in appetite

Not known: hypoglycaemia

General disorders:

Common: fatigue

Immune system disorders:

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; email: medsafety@hpra.ie

4.9 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 haemo-filtration. Therefore, treatment of acute intoxication with TRAMADOL with haemodialysis or haemo-filtration alone is not suitable for detoxification.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: other opioids; ATC code: N02 AX02

Tramadol is a centrally acting opioid analgesic. It is a non-selective pure agonist at mu, delta and kappa opioid receptors with a higher affinity for the mu receptor. Other mechanisms which may contribute to its analgesic effect are inhibition of neuronal reuptake 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. Also gastrointestinal motility is less affected. Effects on the cardiovascular system tend to be slight. The potency of tramadol is reported to be 1/10 (one tenth) to 1/6 (one sixth) that of morphine.

Paediatric population

Effects of enteral and parenteral administration of tramadol have been investigated in clinical trials involving more than 2000 paediatric patients ranging in age from neonate to 17 years of age. The indications for pain treatment studied in those trials included pain after surgery (mainly abdominal), after surgical tooth extractions, due to fractures, burns and traumas as well as other painful conditions likely to require analgesic treatment for at least 7 days.

At single doses of up to 2 mg/kg or multiple doses of up to 8 mg/kg per day (to a maximum of 400 mg per day) efficacy of tramadol was found to be superior to placebo, and superior or equal to paracetamol, nalfurphine, pethidine or low dose morphine. The conducted trials confirmed the efficacy of tramadol. The safety profile of tramadol was similar in adult and paediatric patients older than 1 year (see section 4.2)

5.2 Pharmacokinetic properties

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

The first-pass effect after oral administration is a maximum of 30 %. Tramadol has a high tissue affinity ($V_d, \beta = 203 + 40 l$). It has a plasma protein binding of about 20 %.

Following a single oral dose administration of tramadol 100 mg as capsules or tablets to young healthy volunteers, plasma concentrations were detectable within approximately 15 to 45 minutes within a mean C_{max} of 280 to 208 mcg/L and T_{max} of 1.6 to 2h.

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).

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

In human's 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 substance 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. Up to now, clinically relevant interactions have not 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 ± 9.4 h (Odesmethyltramadol), 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.

Tramadol has a linear pharmacokinetic profile within the therapeutic dosage 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.

Paediatric population

The pharmacokinetics of tramadol and O-desmethyltramadol after single-dose and multiple-dose oral administration to subjects aged 1 year to 16 years were found to be generally similar to those in adults when adjusting for dose by body weight, but with a higher between-subject variability in children aged 8 years and below.

In children below 1 year of age, the pharmacokinetics of tramadol and O-desmethyltramadol have been investigated, but have not been fully characterized. Information from studies including this age group indicates that the formation rate of O-desmethyltramadol via CYP2D6 increases continuously in neonates, and adult levels of CYP2D6 activity are assumed to be reached at about 1 year of age. In addition, immature glucuronidation systems and immature renal function may result in slow elimination and accumulation of O-desmethyltramadol in children under 1 year of age.

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 investigations showed no evidence of any substance-related changes. Central nervous manifestations only occurred after high doses considerably above the therapeutic range: restlessness, salivation, convulsions, and reduced weight gain. 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 reactions.

In rats tramadol dosages from 50 mg/kg/day upwards caused toxic effects in dams and raised neonate mortality. In the offspring retardation occurred in the form of ossification disorders and delayed vaginal and eye opening. Male fertility was not affected. After higher 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 tumourigenic 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 adenomas in male animals (a dose dependent, non-significant increase from 15mg/kg upwards) and an increase in pulmonary tumours in females of all dosage groups (significant, but not dose-dependent)

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The capsule core contains:

Calcium hydrogen phosphate, dihydrate
Magnesium Stearate
Colloidal Silica anhydrous

The capsule shell contains:

Gelatin
Titanium dioxide (E171)

The printing ink contains:

Shellac (E904)
Black Iron Oxide (E172)
Soya Lecithin (E322)
Antifoam (DC 1510)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC/aluminium foil blister packs of 30 or 100 capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

None.

7 MARKETING AUTHORISATION HOLDER

Relon Chem Limited
27 Old Gloucester Street
London
WC1 3XX
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA1128/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th March 2008

Date of last renewal: 24th September 2012

10 DATE OF REVISION OF THE TEXT

March 2020