

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tradol SR 200 mg Prolonged Release Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged release tablet contains 200 mg of Tramadol Hydrochloride.

Excipient with known effect: each tablet contains 118.0mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tablet.

Flat, round, bi-layer tablets. Initial layer white, slow release layer green with one-sided identification mark ^{TR}/200R.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of moderate to severe pain.

4.2 Posology and method of administration

Route of Administration: Oral

The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient. The lowest effective dose for analgesia should generally be selected. The total daily doses of 400mg tramadol hydrochloride should not be exceeded, except in special clinical circumstances.

Unless otherwise prescribed. Tradol SR should be administered as follows:

Adults and adolescents above the age of 12 years

The usual initial dose is 50-100 mg tramadol hydrochloride twice daily, morning and evening. If pain relief is insufficient, the dosage may be titrated upwards to 150 mg or 200 mg tramadol hydrochloride twice daily.

Children

Tradol SR is not suitable for children below the age of 12 years.

Older 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.

Patients with renal insufficiency/dialysis and hepatic impairment

In patients with renal and/or hepatic insufficiency the elimination of tramadol is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements. In cases of severe renal and/or severe hepatic insufficiency tramadol hydrochloride prolonged-release tablets are not recommended.

Method of administration

The tablets are to be taken whole, not divided or chewed, with sufficient liquid, with or without food.

Duration of administration

Tramadol should under no circumstances be administered for longer than absolutely necessary. If long term pain treatment with Tradol SR 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.

4.3 Contraindications

TRADOL SR 200 is contraindicated

- in hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- in acute intoxication with alcohol, hypnotics, analgesics, opioids or other psychotropic medicinal products
- in patients who are receiving monamine oxidase 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, severe impairment of hepatic and renal function and in patients prone to convulsive disorders.

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

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. At therapeutic doses respiratory depression has infrequently been reported.

Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of tramadol hydrochloride exceed the recommended upper daily dose limit (400mg). 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 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 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 antagonist, tramadol cannot suppress morphine withdrawal symptoms.

At therapeutic doses withdrawal symptoms have been reported at a frequency of 1 in 8,000. Reports of dependence and abuse have been less frequent. Because of this potential the clinical need for continued analgesic treatment should be reviewed regularly.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Tramadol should not be combined with MAO inhibitors (see Section 4.3). In patients treated 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 functions 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 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. 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 inducers) may reduce the analgesic effect and shorten the duration of action as a result of a reduction in serum levels of tramadol and its active metabolite.

Other morphine derivatives (including anti-tussives, substitution treatments), benzodiazepines, barbiturates; increased risk of respiratory depression, that may be fatal in overdose.

Mixed agonists/antagonists (e.g. buprenorphine, nalbuphine, pentazocine); the analgesic effect of tramadol, which is a pure agonist, may be reduced and a withdrawal syndrome may occur.

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.

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 antidepressant 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 $>38^{\circ}\text{C}$ and inducible or ocular clonus.

Withdrawal of the serotonergic drugs usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

Caution should be exercised when commencing and 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. Teratogenic effects were not observed. 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. Tradol SR is not recommended during breast feeding. After a single administration of tramadol it is not usually necessary to interrupt breast-feeding.

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 ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1,000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1,000$), very rare ($< 1/10,000$) Not known: cannot be estimated from the available data.

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

Investigations:

Rare: increase in blood pressure

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.

Metabolism and nutrition disorders

Rare: changes in appetite

Not known: hypoglycaemia

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.

Nervous system disorders:

Very common: dizziness

Common: headache, somnolence

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

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).

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 drug withdrawal syndrome, 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: constipation, dry mouth, vomiting

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

Skin and subcutaneous tissue disorders:

Common: hyperhidrosis

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

Musculoskeletal, connective tissue disorders:

Rare: motorial weakness

Hepatobiliary disorders:

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

Renal and urinary disorders:

Rare: micturition disorders (dysuria and urinary retention)

Immune system disorders:

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

General disorders:

Common: fatigue

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; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms

In principle, on intoxication with tramadol symptoms similar to those of 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 TRADOL SR with haemodialysis or haemofiltration alone is not suitable for detoxification.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Codes: Analgesics
N02AX02: Other opioids

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.

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 non-metabolised 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 ($V_{d,\beta} = 203 \pm 40\text{l}$). It has a plasma protein binding of about 20%.

After administration of tramadol 100mg the peak plasma concentration $C_{\text{max}} = 141 \pm 40\text{ng/ml}$ is reached after 4.9 h. After administration of tramadol 200mg $C_{\text{max}} 260 \pm 62\text{ng/ml}$ is reached after 4.8 hours.

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 6h, 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 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 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 (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 19.5h 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 100-300ng/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 investigations showed no evidence of any substance-related changes. Central 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 20mg/kg and 10mg/kg body weight respectively, and dogs rectal doses of 20mg/kg body weight without any reactions.

In rats tramadol dosages from 50mg/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 50mg/kg/day upwards) females exhibited a reduced pregnancy rate. In rabbits there were toxic effects in dams from 125mg/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 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

Lactose Monohydrate
 Hypromellose
 Povidone (kollidon 25)
 Green Varnish
 (Containing: indigotine (E132), quinoline yellow (E104), water, aluminium hydroxide)
 Calcium Hydrogen Phosphate Dihydrate
 Maize Starch
 Microcrystalline Cellulose
 Sodium Starch Glycollate (Type A)
 Magnesium Stearate
 Colloidal Anhydrous Silica
 Hydrogenated Caster Oil

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Tradol SR 200mg Tablets are packed in blisters of non-toxic polypropylene welded on an internally film-coated aluminium semi-rigid support.

Sales packs of 30 and 60 tablets are available.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Limited
Bantry
County Cork

8 MARKETING AUTHORISATION NUMBER

PA 0711/029/007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9 September 2005

Date of last renewal: 9 September 2010

10 DATE OF REVISION OF THE TEXT

August 2015