TRAMAL SR
(Tramadol hydrochloride Ph. Eur.)

100 mg

Tablet

COMPOSITION

Each Tramal Sustained Release film coated tablet contains:
Tramadol Hydrochloride Ph. Eur. …….. 100 mg

THERAPEUTIC INDICATIONS

The treatment of moderate to severe pain.

DOSAGE AND ADMINISTRATION

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.

Adults and adolescents above the age of 12 years:

The recommended doses are intended as a guideline. Patients should always receive the lowest dose that provides effective pain control. Chronic pain management should be preferably given on a fixed dosing schedule.

The starting dose is usually 100 mg tramadol hydrochloride as prolonged-release tablet twice daily, in the morning and in the evening. If the pain relief is not sufficient, the dose may be increased to 150 mg twice daily or 200 mg twice daily.

The dose interval must not be less than 8 hours.

A total daily dose of 400 mg of tramadol hydrochloride should not be exceeded except in special clinical circumstances.

Tramadol hydrochloride should never be used longer than absolutely necessary for pain control. If the nature and severity of the underlying disease suggest the need for prolonged pain management, continued medical need for tramadol hydrochloride analgesia should be reviewed carefully at short, regular intervals (with breaks in treatment if necessary).

Pediatric population

Tramadol prolonged-release tablets are not suitable for children under 12 years of age.

Elderly

A dose adjustment is not usually necessary in patients up to 75 years without clinically manifest hepatic or renal insufficiency. In elderly people over 75 years elimination may be prolonged. Therefore, if necessary, the dose 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 patients' prolongation of the dose 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 prolonged-release tablets must be swallowed whole, not divided or chewed, with sufficient liquid, irrespective of mealtimes.

CONTRAINDICATIONS

Tramadol Tablets are contraindicated:

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

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Tramadol hydrochloride 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,
- renal and hepatic impairment.

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

CYP2D6 metabolism

Tramadol is metabolized 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 metabolizer 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 metabolizers in different populations are summarized 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	6.00%

Post-operative use in children

There have been reports in the published literature that tramadol given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnea, 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.

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 hydrochloride should only be carried out for short periods under strict medical supervision.

Tramadol hydrochloride 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.

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 (400 mg). In addition, tramadol may increase the seizure risk in patients taking other medicinal products that can lower the seizure threshold. Patients with a history of epilepsy or those susceptible to seizures should only be treated with tramadol hydrochloride if there are compelling circumstances.

Care should be taken when treating patients with respiratory depression, or if concomitant CNS-depressant medicinal products are being administered

or if the recommended dose is significantly exceeded as the possibility of respiratory depression cannot be excluded in these situations.

Risk from concomitant use of sedative medicinal products such as benzodiazepines or related medicinal products

Concomitant use of tramadol and sedative medicinal products such as benzodiazepines or related medicinal products may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative 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 sedative medicinal products, the lowest effective dose should be used, and the duration of 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.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per prolonged-release tablet, that is to say essentially 'sodium-free'.

DRUG INTERACTIONS

Tramadol should not be combined with MAO inhibitors.

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.

The concomitant use of opioids with sedating medicinal products such as benzodiazepines or related substances increases 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.

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 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 serotoninergic 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 Odemethylated metabolite. The clinical importance of such an interaction has not been studied.

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.

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.

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Tramadol - administered before or during birth - does not affect uterine contractility.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breast-feeding

Administration to nursing women is not recommended as Tramadol may be secreted in breast milk and may cause respiratory depression in the infant.

Fertility

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

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.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

• The medicine is likely to affect your ability to drive
• Do not drive until you know how the medicine affects you
• It is an offence to drive while under the influence of this medicine
• However, you would not be committing an offence (called 'statutory defence') if:
  - The medicine has been prescribed to treat a medical or dental problem and
  - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
  - It was not affecting your ability to drive safely

ADVERSE DRUG REACTIONS

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

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, dyspnea

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.

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.

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 behavior, perception disorders).

Not known: Drug dependence.

Eye disorders:

Rare: miosis, mydriasis, blurred vision

Gastrointestinal disorders:

Very common: nausea

Common: vomiting, constipation, dry mouth

Uncommon: retching; gastrointestinal irritation (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 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)

Immune system disorders:

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

General disorders:

Common: fatigue

Uncommon: drug withdrawal syndrome. 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, paraesthesias, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalization, derealization, paranoia).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 at pv@searlecompany.com

OVERDOSE

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

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 formulation.

Tramadol is minimally eliminated from the serum by hemodialysis or haemo-filtration. Therefore, treatment of acute intoxication with tramadol with hemodialysis or hemofiltration alone is not suitable for detoxification.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: other opioids

ATC code: N02A X02

Mechanism of action

Tramadol is an atypical opioid analgesic that acts on the central nervous system. 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 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.

Pediatric population

Effects of enteral and parenteral administration of tramadol have been investigated in clinical trials involving more than 2000 pediatric 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, nalbuphine, pethidine or low dose morphine. The conducted trials confirmed the efficacy of tramadol. The safety profile of tramadol was similar in adult and pediatric patients older than 1 year.

Pharmacokinetic properties

Absorption

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-metabolized available tramadol is probably due to the low first-pass effect. The first-pass effect after oral administration is a maximum of 30 %.

Distribution

Tramadol has a high tissue affinity (V d,ß = 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

Elimination half-life t1/2,ß 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 humans' tramadol is mainly metabolized 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 t1/2,ß (6 healthy volunteers) is 7.9 h (range 5.4 - 9.6 h) and is approximately that of tramadol.

Biotransformation

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.
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 19.5 h and 43.2 h respectively.

Linearity/non-linearity

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.

Pediatric 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 Odesmethyltramadol 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.

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, hematological, 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 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 tumors. 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 tumors in females of all dosage groups (significant, but not dose-dependent).

PRESENTATION

Tramal SR Tablets are available as a Box of 1 x 10 tablets.

INSTRUCTIONS

- To be sold on the prescription of a registered medical practitioner only.
- Store below 30°C.
- Protect from sunlight and heat.
- Keep all medicines out of sight and reach of children.

REGISTRATION NUMBER

Tramal SR Tablets: 023317 (Mfg. U.S.P. Specs)
Manufacturing License No: 000016

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Manufactured by:

The Searle Company Limited,

F-319, S.I.T.E., Karachi-Pakistan. 1012001977

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