

1.3

Product Information

1.3.1

Summary of Product Characteristics (SmPC)

1.3.1 Summary of Product Characteristics (SmPC)**1. Name of the Brand name of product**

GREMADOL(Tramadol Hydrochloride Injection BP 50 mg/ml)

2. Generic Name : Tramadol Hydrochloride Injection 50mg/ml**3. Qualitative and quantitative composition**

Each ml contains:

Tramadol Hydrochloride BP 50 mg

Water for Injection BP q.s.

4. Pharmaceutical form

Liquid Injection

5. Pharmacodynamic properties:**Pharmacological Properties:**

Tramadol Hydrochloride Injection 50 mg/ml is a centrally acting 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.

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 ($V_d, \beta = 203 + 40 \text{ l}$). 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 $t_{1/2}$, β 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 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 $t_{1/2}$, β (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 19.5 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.

5. Posology and method of administration**Dosage and Administration**

Parenteral

Moderate to severe pain

Adult: IM/IV inj over 2-3 min/IV infusion: 50-100 mg given every 4-6 hr.

Elderly: Lower initial dose. Max: 300 mg daily (>75 yr).

CrCl (ml/min) Dosage Recommendation

10-<30 Increase dosage interval to 12 hr.

<10 Contraindicated.

Hepatic impairment: Severe: Increase dosage interval to 12 hr.

Parenteral

Postoperative pain

Adult: IM/IV inj over 2-3 min/IV infusion: Initially, 100 mg followed by 50 mg every 10-20 min if necessary up to 250 mg for the 1st hr.

Maintenance: 50-100 mg every 4-6 hr. Max: 600 mg daily.

Elderly: Lower initial dose. Max: 300 mg daily (>75 yr).

CrCl (ml/min) Dosage Recommendation

10-<30 Increase dosage interval to 12 hr.

<10 Contraindicated.

Hepatic impairment: Severe: increase dosage interval to 12 hr.

Rectal

Moderate to severe pain

Adult: 100 mg suppository up to 4 times daily.

Elderly: Lower initial dose. Max: 300 mg daily (>75 yr).

CrCl (ml/min) Dosage Recommendation

<30 Increase dosage interval to 12 hr.

<10 Contraindicated.

Hepatic impairment: Severe: Increase dosage interval to 12 hr.

Special Populations: A dosage interval of 12 hrs is recommended in severe hepatic impairment.

6. Contraindication

Tramadol Hydrochloride Injection 50 mg/ml should not be given to patients who have previously demonstrated hypersensitivity towards tramadol or any of the other ingredients. Tramadol Hydrochloride Injection 50 mg/ml should not be given to patients

suffering from acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs.

In common with other opioid analgesics, tramadol should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal.

Tramadol Hydrochloride Injection 50 mg/ml is contraindicated in patients with epilepsy not adequately controlled by treatment.

Tramadol must not be used in narcotic withdrawal treatment.

7. Special warning and special precaution for use

Warnings

At therapeutic doses, tramadol has the potential to cause withdrawal symptoms. Rarely, cases of dependence and abuse have been reported.

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.

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 should be for short periods and under strict medical supervision.

Tramadol Hydrochloride Injection 50 mg/ml is not a suitable substitute in opioid dependent patients. The product does not suppress morphine withdrawal symptoms although it is an opioid agonist.

Tramadol Hydrochloride Injection 50 mg/ml may cause drowsiness and this effect may be potentiated by alcohol and other CNS depressants. Ambulant patients should be warned not to drive or operate machinery if affected.

Precautions

Tramadol Hydrochloride Injection 50 mg/ml should be used with caution in opioid-dependent patients, patients with head injury, 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 or in shock. In patients sensitive to opiates the product should only be used with caution.

Convulsions have been reported at therapeutic doses and the risk may be increased at doses exceeding the usual upper daily dose limit. Patients with a history of epilepsy or those susceptible to seizures should only be treated with

Tramadol if there are compelling reasons. The risk of convulsions may increase in patients taking tramadol and concomitant medication that can lower the seizure threshold.

Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered, or if the recommended dosage is significantly exceeded, as the possibility of respiratory depression cannot be excluded in these situations. At therapeutic doses respiratory depression has infrequently been reported.

In one study using a nitrous oxide/opioid (tramadol) anaesthetic technique (with only intermittent administration of enflurane 'as required') tramadol was reported to enhance intra-operative recall. Hence its use during potentially very light planes of general anaesthesia should be avoided.

Two studies of tramadol administration during anaesthesia comprising continuous administration of isoflurane have shown clinically significant lightening of anaesthetic depth or intra-operative recall. Therefore, providing the current practice of administering continuous, potent (volatile or intravenous) anaesthetic agent is followed; tramadol may be used intra-operatively in the same way as other analgesic agents are routinely used.

This medicinal product contains approximately 8.29mg sodium acetate trihydrate (1.4mg sodium) per 2ml dose.

8. Interaction with other medicinal products and form of interaction

Concomitant administration of Tramadol Hydrochloride Injection 50 mg/ml with other centrally acting drugs, including alcohol, may potentiate CNS depressant effects.

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.

Theoretically there is a possibility that tramadol could interact with lithium. There have been no reports of this potential interaction.

Concomitant therapeutic use of tramadol and serotonergic drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors, 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 drugs usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

There have been isolated reports of interaction with coumarin anticoagulants resulting in an increased INR with major bleeding and ecchymoses in some patients and so care should be taken when commencing treatment with tramadol in patients on anticoagulants.

Pharmacokinetic studies were conducted to investigate the effects of cimetidine, quinidine and carbamazepine on the pharmacokinetics of tramadol.

Carbamazepine— The simultaneous administration of carbamazepine markedly decreases serum concentrations of tramadol to an extent that a decrease in analgesic effectiveness and a shorter duration of action may occur.

Cimetidine - With the concomitant or previous administration of cimetidine clinically relevant interactions are unlikely to occur. Therefore, no alteration of the tramadol dosage regimen is recommended for patients receiving chronic cimetidine therapy.

Quinidine - A study in 12 healthy volunteers has shown that quinidine causes an approximate 25% increase in the tramadol C_{max} and AUC; T_{max} is unaffected. However, the increases in C_{max} and AUC fall within the normal therapeutic range for tramadol, and no dosage adjustment is required.

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.

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.

9. Pregnancy and lactation

Pregnancy

Animal studies with tramadol at very high doses have revealed 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 50mg/ml Solution for Injection 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.

Lactation

Tramadol and its metabolites are found in small amounts in human breast milk. An infant could ingest 0.1% of the dose given to the mother. Tramadol Hydrochloride Injection 50 mg/ml should not be administered during breast-feeding. After a single administration of tramadol however, it is not usually necessary to interrupt breast feeding.

10. Effects on ability to drive and use machines

Tramadol Hydrochloride Injection 50 mg/ml may cause somnolence and dizziness and these effects may be potentiated by alcohol and other CNS depressants. Ambulant patients should be warned not to drive or operate machinery if affected.

11. Undesirable effects

Rapid intravenous administration may be associated with a higher incidence of adverse effects and therefore should be avoided. The most commonly reported adverse drug 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 system disorders:

Uncommon: cardiovascular regulation (palpitation, tachycardia, postural hypotension or cardiovascular collapse). These adverse effects may occur especially after intravenous administration and in patients who are physically stressed.

Rare: bradycardia, increase in blood pressure.

Nervous system disorders:

Very common: dizziness.

Common: headache, somnolence.

Rare: changes in appetite, paraesthesia, tremor, respiratory depression, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope.

Not known: speech disorders.

If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly, respiratory depression may occur.

Epileptiform 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, anxiety and nightmares. Psychic side effects may occur following administration of tramadol, which vary individually in intensity and nature (depending on personality and duration of medication). These include changes in mood (usually elation, occasionally dysphoria), changes in activity (usually suppression, occasionally increase) and changes in cognitive and sensorial ability (e.g. decision behaviour, perception disorders). Dependence may occur.

Eye disorders:

Rare; blurred vision

Not known: mydriasis.

Respiratory system disorders:

Rare: dyspnoea.

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 irritation (a feeling of pressure in the stomach, bloating), diarrhea.

Skin and subcutaneous disorders:

Common: sweating.

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

Musculo-skeletal system disorders:

Rare: muscle weakness.

Hepatobiliary system 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 system disorders:

Rare: micturition disorders (difficulty in passing urine, dysuria and urinary retention)

General disorders:

Common: fatigue.

Rare: allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis. 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, paraesthesias, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, personalisation, derealisation, paranoia).

12. 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, and 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.

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

13. Pharmaceutical particulars

13.1 List of excipients

- Disodium Edetate BP
- Sodium Citrate BP

- Sodium Citrate BP
- Citric Acid BP
- Water for Injection BP

14. Shelf life

36 months.

15. Special precautions for storage

Store in a cool, dark place, below 25°C.

16. Nature and contents of container

2 ml clear glass ampoule.

17. Instruction for use handling and disposal

Keep out of reach of children.

18. Manufacturer BY

Alpa Laboratories Limited

33/2 A.B Road, Pigdambar, Indore (MP) Pin

Code- 453446

+91 731 4294567

+91 731 4294444

19. Marketing authorisation holder

M/S. GREENLIFE PHARMACEUTICALS LTD.
, 2, BANK LANE, OFF TOWN PLANNING
WAY, ILUPEJU, LAGOS, NIGERIA