Cadirax® Capsule

Tramadol Hydrochloride 50 mg

This information is intended for use by health professionals.

1. **Name of the medicinal product**
   Cadirax® Capsule (Tramadol Hydrochloride 50 mg)

1. **Qualitative and quantitative composition**
   Each capsules contains 50 mg of Tramadol Hydrochloride

2. **Pharmaceutical form**
   Capsules

3. **Clinical parameters**

3.1. Therapeutic indications

For treatment and prevention of moderate to severe pain

3.2. Posology and method of administration

As with all analgesic drugs, the dose of Cadirax® Capsule 50mg capsules should be adjusted according to the severity of the pain and the clinical response of the individual patient

Adults and children aged 12 years and over

Oral administration:

Acute pain:

An initial dose of 100 mg is usually necessary. This can be followed by doses of 50 or 100 mg 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 50 mg and then titrate dose according to pain severity. The need for continued treatment should be assessed at regular intervals as withdrawal symptoms and dependence have been reported (see section 4.4 Special warnings and special precautions for use). A total daily dose of 400 mg should not be exceeded except in special clinical circumstances.

***Elderly*:**

The usual dosages may be used although it should be noted that in volunteers aged over 75 years the elimination half-life of tramadol was increased by 17% following oral administration.

Renal impairment/renal dialysis:

The elimination of tramadol may be prolonged. The usual initial dosage should be used. For patients with creatinine clearance < 30 ml/min, the dosage interval should be increased to 12 hours. Tramadol is not recommended for patients with severe renal impairment (creatinine clearance < 10 ml/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 under 12 years:

Not recommended.

3.3. Contradictions

Cadirax® 50 mg capsules should not be administered to patients who have previously demonstrated hypersensitivity to it or in cases of acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic

drugs. In common with other opioid analgesics it should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal. Tramadol must not be administered during breastfeeding if long term treatment, i.e. more than 2 to 3 days, is necessary (section 4.6). Cadirax® 50 mg capsules is contraindicated in patients with epilepsy not adequately controlled by treatment and for use in narcotic withdrawal treatment.

3.4. Special warnings and precautions for use

Warnings:

At therapeutic doses, Cadirax® 50 mg capsules 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 reporting 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.

In patients with a tendency to drug abuse or dependence, treatment should be for short periods and under strict medical supervision.

Cadirax® 50 mg is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, it cannot suppress morphine withdrawal symptoms.

Precautions:

Cadirax® 50 mg capsule should be used with caution in patients with head injury, increased intracranial pressure, severe impairment of hepatic and renal function and in patients prone to convulsive disorders or in shock.

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 (see section 4.5) Interaction with other medicinal products and other forms of interaction). Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered, 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 recent studies of tramadol administration during anaesthesia comprising continuous administration of isoflurane did not show clinically significant lightening of anaesthetic depth or intra-operative recall. Therefore providing the current practice of administering continuous, potent (volatile or intravenous) anaesthetic agents is followed, Ethypharm Tramadol may be used intra-operatively in the same way as other analgesic agents are routinely used.

The ingredient aspartame contains a source of phenylalanine which may be harmful to people with phenylketonuria.

3.5. Interaction with other medicinal products and other forms of interaction

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

Simultaneous administration with cimetidine is associated with clinically insignificant changes in serum concentrations of tramadol. Therefore no alteration of the Cadirax® 50 mg capsules regimen is recommeded for patient -s receiving chronic cimetidine therapy.

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.

Tramadol may increase the potential for both selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) to cause convulsions (see sections 4.4 Special warnings and special precautions for use and 5.2 Pharmacokinetic properties).
There is a theoretical possibility that tramadol could interact with lithium. There have been no reports of this potential interaction.

The analgesic effect of tramadol is in part mediated by inhibition of the re-uptake of norepinephrine and enhancement of the release of serotonin (5-HT). In studies the pre- or postoperative application of the antiemetic 5-HT3 antagonist ondansetron increased the requirements of tramadol in patients with postoperative pain.

3.6. Pregnancy and lactation

Pregnancy:
In humans, there are no sufficient data to assess malformative effect of tramadol when given during the first trimester of pregnancy. Animal studies have not shown any teratogenic effects, but at high doses, foetotoxicity due to maternotoxicity appeared (See 5.3 Preclinical data).

Tramadol crosses the placenta, therefore as with other opioid analgesics, chronic use of tramadol during the third trimester may induce a withdrawal syndrome in newborn. At the end of pregnancy, high dosages, even for short term treatment, may induce respiratory depression in new-born. There is inadequate evidence available on the safety of tramadol in human pregnancy, therefore Tramadol Hydrochloride 50 mg capsules should not be used in pregnant woman.

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 50 mg capsules should not be administered during breast feeding.

3.7. Effects on ability to drive and use machines

Cadirax® 50mg capsules 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.

3.8. Undesirable effects

***Gastrointestinal system*:**

Nausea, vomiting and occasionally dry mouth. Both diarrhoea and constipation have been reported. In controlled trials the incidence of constipation is lower than that of comparator agents.

Central nervous system and psychiatric:
Tiredness, fatigue, drowsiness, somnolence, dizziness, headache, confusion, hallucinations and infrequently respiratory depression. Dependence, dysphoria and convulsions have been reported rarely (see section 4.5 Interactions).

***Physical dependence*:**

Dependence, abuse and withdrawal reactions have been reported. Typical opiate withdrawal reactions include agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms (see sections 4.4 Special warnings and special precautions for use and 4.2 Posology and method of administration).

Allergic/anaphylactoid reaction:

Dyspnoca, wheezing, broncho spasm and worsening of existing asthma.

Other adverse events:

Diaphoresis, urticaria and pruritus have been reported. Skin rashes, tachycardia, orthostatic hypotension, increase in blood pressure, bradycardia, flushing,

syncope and anaphylaxis have been rarely reported. Cases of blood dyscrasias have been rarely observed during treatment with tramadol, but causality has not been established.

3.9. Overdose

Symptoms of overdosage are typical of other opioid analgesics, and include miosis, vomiting, cardiovascular collapse, sedation and coma, seizures and respiratory depression.

Supportive measures such as maintaining the patency of the airway and maintaining cardiovascular function should be instituted; naloxone should be used to reverse respiratory depression; fits can be controlled with diazepam.

Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore treatment of acute intoxication with Tramadol Hydrochloride 50mg capsules with haemodialysis or haemofiltration alone is not suitable for detoxification.

5.0. Pharmacological Properties

5.1. Pharmacodynamic properties

Cadirax® 50mg capsules 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.

5.2. Pharmacokinetic properties

The half-life of the terminal elimination phase (t½ c) was 6.0 ± 1.5 hours in young volunteers. Tramadol pharmacokinetics show little age dependence in volunteers up to the age of 75 years. In volunteers aged over 75 years, t ½ c was 7.0 ± 1.6 hours on oral administration.

Since tramadol is eliminated both metabolically and renally, the terminal half-life t½ c may be prolonged in impaired hepatic or renal function. However, the increase in the t½ c values is relatively low if at least one of these organs is functioning

normally. In patients with liver cirrhosis t ½ c tramadol was a mean of 13.3 ± 4.9 hours; in patients with renal insufficiency (creatinine clearance ä 5 ml/min) it was 11.0 ± 3.2 hours.

5.3. Preclinical safety data

In single and repeat-dose toxicity studies (rodents and dogs) exposure to tramadol 10 times that expected in man is required before toxicity (hepatotoxicity) is observed. Symptoms of toxicity are typical of opioids and include restlessness, ataxia, vomiting, tremor, dyspnea and convulsions.

Exposure to tramadol (> that expected in man), in lifetime toxicity studies in rodents did not reveal any evidence of carcinogenic hazard, and a battery of in-vitro and in-vivo mutagenicity tests were negative.

No teratogenic effects have been observed in animal tests (rat and rabbit: the dosage of Tramadol given has been up to seven times higher than the dosage given to humans). Minimal embryo toxic effects (delayed ossification) were observed in the tests. No effect was observed on the fertility or the development of the offspring in the tests.

6.0. Pharmaceutical Particulars

6.1. List of excipients

Corn starch

Lactose

Magnesium stearate

6.2. Incompatibles

None known

6.3. Shelf life

3 years

6.4 Special precaution for storage

Store in the original package

6.5 Nature of contents of container

Blister packs boxes of 10 capsules.

6.6. Special precautions for disposals

No special requirements

7. Marketing Authorization Holder

Nemel Pharmaceuticals Limited, Enugu.

8. Marketing Authorization Number(S)

Not applicable

9. Date of first authorization/renewal of the authorization

Not applicable

10. Date of revision of the text

Not applicable