For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

DOMADOL

1. Generic Name

Tramadol Hydrochloride Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DOMADOL 50 mg

Each ml contains:

Tramadol Hydrochloride I.P. ……50 mg

Water for Injection I.P. ……. q.s.

The excipients used are Citric Acid Anhydrous, Sodium Citrate and Water for Injection.

DOMADOL 100 mg

Each 2 ml contains:

Tramadol Hydrochloride I.P. ……100 mg

Water for Injection I.P. ……. q.s.

The excipients used are Citric Acid Anhydrous, Sodium Citrate and Water for Injection.

3. DOSAGE FORM AND STRENGTH

DOSAGE FORM: Injection

STRENGTH: 50 mg/100 mg

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

Analgesic- For severe acute and chronic pain, diagnostic measures and surgical pain.

4.2 Posology and Method of Administration

Dosage: As directed by the Physician

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

Unless otherwise prescribed, DOMADOL should be administered as follows:

Adults and adolescents above the age of 12 years:

The usual dose is 50 or 100mg 4-6 hourly by the intravenous or intramuscular route. Dosage should be adjusted according to pain severity and response.

Intravenous injections must be given slowly over 2-3 minutes.

For post-operative pain administer an initial bolus of 100mg. During the 60 minutes following the initial bolus, further doses of 50mg may be given every 10-20 minutes, up to a

total dose of 250mg including the initial bolus. Subsequent doses should be 50mg or 100mg 4-6 hourly up to a total daily dose of 400mg.

Children

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

Geriatric patients

A dose adjustment is not usually necessary in elderly 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 Insufficiency

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.

Method of administration

DOMADOL may be administered intramuscularly, by slow intravenous injection, or diluted in solution for administration by infusion or patient controlled analgesia.

Duration of administration

DOMADOL should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with DOMADOL is necessary in view of the nature and severity of the illness, then careful 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

DOMADOL is contraindicated

- in patients who have previously shown hypersensitivity to the active substance tramadol or to any of the excipients.
- in patients suffering from acute intoxication with alcohol, hypnotics, analgesics, opioids, or psychotropic medicinal products.
- in patients who are receiving monoamine oxidase (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.

4.4 Special Warnings and Precautions for Use

DOMADOL 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.

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.

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

Tolerance, psychological 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.

DOMADOL is not a suitable 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 post-operatively 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.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs

Concomitant use of DOMADOL and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe DOMADOLconcomitantly with sedative medicines, 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.

Do not use if solution is not clear or has suspended matter.

Tramadol should be used for severe acute pain only for a period not exceeding 5 days

4.5 Drugs Interactions

DOMADOL 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 DOMADOL.

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 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, 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.

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.

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.

The administration of DOMADOL with other centrally depressant medicinal products, including alcohol, may potentiate the CNS effects.

Sedative medicines such as benzodiazepines or related drugs

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited.

4.6 Use in Special Populations (Such as Pregnant Women, Lactating Women, Paediatric Patients, Geriatric Patients Etc.)

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, DOMADOL 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

Approximately 0.1 % of the maternal dose is excreted into the milk. In the immediate post-partum period, for maternal oral daily dosage up to 400 mg, this corresponds to a mean amount of tramadol ingested by breast-fed infants of 3% of the maternal weight-adjusted dosage. For this reason, tramadol should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not necessary following a single dose of tramadol.

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, DOMADOL may cause effects such as somnolence and dizziness and therefore may impair a patient's ability to drive safely or operate machinery. This applies particularly in conjunction with alcohol and other psychotropic substances. Patients should, therefore, not drive or operateS machinery.

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

4.8 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 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, respiratory depression may occur.

Worsening of asthma has been reported, though a causal relationship has not been established.

Not known: Hiccups

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

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. Psychological adverse reactions may occur following administration of DOMADOL 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). 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, paresthesias, 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 irritation (a feeling of pressure in the stomach, bloating), diarrhoea

Skin and subcutaneous tissue disorders:

common: sweating

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 (difficulty in passing urine, dysuria and urinary retention)

Immune system disorders:

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

General disorders:

common: fatigue

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.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

Tramadol is a centrally acting analgesic which possesses opioid agonist properties. Tramadol consists of two enantiomers, the (+)-isomer is predominantly active as an opioid with preferential activity for the μ-receptor. The (-)-isomer potentiates the analgesic effect of the (+)-isomer and is active as an inhibitor of noradrenaline and serotonin uptake thereby modifying the transmission of pain impulses.

Tramadol also has an antitussive action. At the recommended dosages, the effects of tramadol given orally on the respiratory and cardiovascular systems appear to be clinically insignificant. The potency of tramadol is reported to be $1/10^{th}$ to $1/6^{th}$ that of morphine.

5.2 Pharmacodynamic Properties

Analgesic, ATC code: N02AX02

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, nalbuphine, 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.

5.3 Pharmacokinetic Properties

a) General

The mean absolute bioavailability after intramuscular administration was found to be 100%.

The distribution of tramadol following intravenous administration is rapid and in two phases with different half-lives of 0.31 ± 0.17 hours (initial rapid phase) and 1.7± 0.4 hours (slower phase) respectively.

After intravenous administration of 100 mg tramadol, the serum concentration was 613 ± 221 ng/ml at 15 minutes' post dosing and 409 ± 79 ng/ml at 2 hours post dosing. Tramadol has a high tissue affinity with an apparent volume of distribution of 203 L after intravenous dosing in healthy volunteers.

Tramadol undergoes hepatic metabolism with approximately 85% of an intravenous dose being metabolised in young healthy volunteers. 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 t½β (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 cytochrome P450 isoenzymes, CYP3A4 and CYP2D6 involved in the metabolism of tramadol, may affect the plasma concentration of tramadol or its active metabolite.

Tramadol is essentially excreted via the kidneys. The mean elimination half-life of tramadol following intravenous administration is 5-6 hours. Total clearance of tramadol was 28.0 L/h following intravenous administration.

b) Characteristics in patients

Effect of age: Tramadol pharmacokinetics show little age-dependence in volunteers up to the age of 75 years. In volunteers aged over 75 years, the terminal elimination half-life was 7.0 ± 1.6 h compared to 6.0 ± 1.5 h in young volunteers after oral administration. Effect of hepatic or renal impairment: As both tramadol and its pharmacologically active metabolite, O-desmethyl tramadol, are eliminated both metabolically and renally, the terminal half-life of elimination (t½) may be prolonged in patients with hepatic or renal dysfunction. However, the increase in t½ is relatively small if either excretory organ is functioning normally. In liver cirrhosis patients, the mean t½ of tramadol was 13.3 ± 4.9 hours. In patients with renal failure (creatinine clearance < 5 mL/min) the t½ of tramadol was 11.0 ± 3.2 hours and that of M1 was 16.9 ± 3.0 hours. Extreme values observed to date are 22.3 hours (tramadol) and 36.0

hours (M1) in liver cirrhosis patients and 19.5 hours (tramadol) and 43.2 hours (M1) in renal failure patients.

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 ates 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 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 indicslow elimination and accumulation of O-desmethyltramadol in children under 1 year of age.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

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 dog's rectal doses of 20 mg/kg body weight without any reactions.

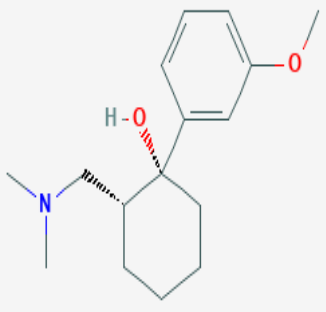
In rats tramadol dosages from 50 mg/kg/day upwards caused toxic effects in dams and raised neonate mortality reported. In the offspring retardation occurred in the form of ossification disorders and delayed vaginal and eye opening. Male fertility was not affected. After higher doses (from 50 mg/kg/day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

7. DESCRIPTION

Tramadol is chemically (1*R*,2*R*)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexan-1-ol having molecular formula of $C_{16}H_{25}NO_2$ and molecular weight is 263.37 and chemical structure is:



Tramadol is a white or almost white crystalline powder which is freely soluble in water and in methanol; very slightly soluble in acetone.

DOMADOL 50 mg

Tramadol Hydrochloride Injection is a clear, colourless liquid, free from particles. The excipients used are Citric Acid Anhydrous, Sodium Citrate and Water for Injection.

DOMADOL 100 mg

Tramadol Hydrochloride Injection is a clear, colourless liquid, free from particles. The excipients used are Citric Acid Anhydrous, Sodium Citrate and Water for Injection.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

None Stated

8.2 Shelf-life

Do not use later than date of expiry

8.3 Packaging information

DOMADOL 50 mg is available in 1 ml ampoules.

DOMADOL 100 mg is available in 2 ml ampoules.

8.4 Storage and Handing Instructions

Store below 30^0C. Protect from light and moisture.

Keep medicine out of reach of children.

9. PATIENT COUNSELLING INFORMATION

Package leaflet: Information for the patient

DOMADOL

Tramadol hydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any questions, or if there is anything you do not understand, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

9.1 What DOMADOL is and what it is used for

Tramadol - the active substance in DOMADOL - is a painkiller belonging to the class of opioids that acts on the central nervous system. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

DOMADOL is used for the treatment of moderate to severe pain.

9.2 What you need to know before you use DOMADOL

Do not use DOMADOL

- If you are allergic to tramadol hydrochloride or any of the other ingredients of this medicine
- Allergic reactions to DOMADOL could include skin rash, swelling of the face, wheezing or difficulty breathing
- If you are epileptic and your fits are not well controlled by treatment
- If the patient is a child under 12 years of age
- If you are pregnant or breast-feeding
- If you are taking any of the following medicines:
- sleeping tablets or tranquillizers such as nitrazepam
- other pain-killers such as codeine ormorphine
- psychotropic medicines such as chlorpromazine
- a monoamine oxidase inhibitor used to treat depression, or if you have
- taken one in the past two weeks
- If you have recently been drinking alcohol.
- It should not be used in narcotic drug withdrawal treatment.

Warnings and Precautions

Tell your doctor before you are given DOMADOL Injection:

- If you have liver or kidney disease. You may need a lower dose or a longer interval between doses
- If you have a head injury or brain disease

- If you have a problem that makes you faint or feel faint
- If you are in a state of shock. You may feel light headed, faint, cold or clammy or look pale
- If you suffer from epilepsy, convulsions or seizures (fits) or have had them in the past
- If you suffer from asthma, other lung diseases or have difficulty in breathing.
- If you think you may be addicted to other pain relievers (opioids)

Tramadol may lead to addiction.

In patients with a tendency to drug abuse, Tramadol Injection should only be given for short periods under strict medical supervision. Tramadol is transformed in the liver by an enzyme. Some people have a variation of this enzyme and this can affect people in different ways. In some people, they may not get enough pain relief but other people are more likely to get serious side effects. If you notice any of the following side effects, you must stop taking this medicine and seek medical advice: slow or shallow breathing, confusion, sleepiness, small pupils, feeling or being sick, constipation, lack of appetite. Use in children with breathing problems Tramadol is not recommended in children with breathing problems, since the symptoms of tramadol toxicity may be worse in these children.

Children and adolescents

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

Use in children with breathing problems

Tramadol is not recommended in children with breathing problems, since the symptoms of tramadol toxicity may be worse in these children.

Other medicines and DOMADOL

Other medicines and Tramadol Tell your doctor if you are taking, or have recently taken, any of the following medicines. This is important because Tramadol Injection could alter how other medicines work.

- Serotonin – norepinephrine reuptake inhibitors (SNRI's) tricyclic antidepressants, antipsychotics and other seizure threshold-lowering medicinal products (such as bupropion, mirtazapine, (tetrahydrocannabinol) to cause convulsions.
- carbamazepine, a treatment for epilepsy, as this may reduce the effectiveness of the tramadol
- triptans, such as sumatriptan, used to treat migraines, as this may increase the effectiveness of the triptans
- coumarin anticoagulants, used to thin the blood, such as warfarin, as this may alter the effectiveness of the anticoagulant
- selective serotonin reuptake inhibitors (SSRI's), used to treat depression, such as fluoxetine, as this may increase the effect of the SSRI's
- lithium, used to treat psychotropic disorders, as this may alter the effect of lithium
- ondansetron, used to prevent nausea and vomiting. Other active substances known to inhibit CYP3A4, such as ketoconazole and and erythromycin, might inhibit the metabolism of Tramadol.The concomitant use of opioids with sedating medicinal products such as benzodiazepines or related products increases the risk of respiratory

depression, sedation, coma and death because of additive CNS depressant effect. The dose of Tramadol and the duration of the concomitant use should be limited.

Tell your doctor if you are taking, have recently taken or might take any other medicines.

The risk of side effects increases

- if you are taking medicines which may cause convulsions (fits), such as certain antidepressants or antipsychotics. The risk of having a fit may increase if you are given Tramadol Injection at the same time. Your doctor will tell you whether Tramadol Injection is suitable for you.
- if you are taking certain antidepressants. Tramadol Injection may interact with these medicines and you may experience symptoms such as involuntary, rhythmic contractions of muscles, including the muscles that control movement of the eye, agitation, excessive sweating, tremor, exaggeration of reflexes, increased muscle tension, body temperature above 38 °C.

Pregnancy and breast feeding:

DOMADOL should not be given during pregnancy or while breast feeding. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Chronic use during pregnancy may lead to withdrawal symptoms in newborns.

Tramadol is excreted into breast milk. For this reason, you should not be given Tramadol more than once during breast-feeding, or alternatively, if you receive Tramadol more than once, you should stop breast-feeding.

Driving and using machines:

DOMADOL may cause drowsiness, dizziness and blurred vision and therefore may impair your reactions and your ability to drive.

- Do not drive while taking this medicine until you know how it affects you.
- It is an offence to drive if this medicine affects your ability to drive.
- However, you would not be committing an offence 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 or in the information provided with the medicine and
- It was not affecting your ability to drive safely

Talk to your doctor or pharmacist if you are not sure whether it is safe for you to drive while taking this medicine.

If you feel that your reactions are affected, do not use electric tools or operate machinery, and do not work without a firm hold!

DOMADOL with alcohol:

Do not drink alcohol during treatment with DOMADOL as its effects may be intensified.

9.3 How to use DOMADOL

Your nurse or doctor will give you the injection or infusion. Your doctor will decide the correct dosage for you and how and when the injection or infusion will be given.

Since the injection or infusion will be given to you by a doctor or nurse, it is unlikely that you will be given too much. If you think you have been given too much, you must tell the person giving you the injection or infusion.

Tramadol Injection should not be given to children under 12 years of age. The dosage should be adjusted to the intensity of your pain and your individual pain sensitivity. In general, the lowest dose.

If you receive too much DOMADOL Injection.

If you think you have been given or have given yourself too much Tramadol Injection, tell a doctor or nurse immediately.

Symptoms of intoxication are 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. to relieve pain should be given for the shortest possible time.

If you stop using DOMADOL

You should not suddenly stop taking this medicine unless your doctor tells you to. If you want to stop taking your medicine, discuss this with your doctor first, particularly if you have been taking it for a long time. Your doctor will advise you when and how to stop, which may be by lowering the dose gradually to reduce the chance of developing unnecessary side effects (withdrawal symptoms). Rarely when some people stop treatment with tramadol they get withdrawal symptoms. These symptoms include agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms. Other symptoms that have rarely been seen with Tramadol discontinuation include: panic attacks, severe anxiety, hallucinations, paraesthesias, tinnitus and unusual CNS symptoms (i.e. confusion, delusions,personalization, derealisation, paranoria)

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common side effects (occurring in more than 1 in 10 patients):

nausea, dizziness

Common side effects(occurring in less than 1 in 10 patients):

- headache, drowsiness, fatigue
- vomiting, constipation, dry mouth, sweating.
- Uncommon side effects (occurring in less than 1 in 100 patients):
- changes in heart beat or rhythm which may make you feeling faint or dizzy
- especially if you stand up quickly
- retching, stomach irritation or feeling bloated
- diarrhoea
- dermal reactions – rash, itching, hives.

- Rare side effects (occurring in less than 1 in 1000 patients):
- changes in appetite, abnormal touch sensations, trembling, difficulty breathing,
- fits, fainting, speech disorders
- slowing of the heart rate, increased blood pressure
- nightmares, disturbed sleep patterns, hallucinations (seeing things), feeling
- confused, changes in mood, activity or awareness, anxiety, delirium
- blurred vision, excessive dilation or constriction of the pupils
- muscle weakness or twitching, abnormal coordination
- increase in liver enzymes
- difficulty or pain passing water (urine)
- worsening of asthma, shortness of breath
- Rarely when some people stop taking tramadol they get withdrawal symptoms.

These symptoms include agitation, nervousness, shaking, hyperactivity and difficulty in sleeping.

Very rarely panic attacks, severe anxiety, hallucinations, tinnitus or abnormal skin sensations, as well as confusion, delusions, personalisation, derealisation and paranoia, have occurred.

Other side effects (frequency unknown):

- low blood sugar levels.
- hypoglycaemia

9.5 How to store DOMADOL

Store below 30^0C. Protect from light and moisture.

Keep medicine out of reach of children

9.6 Contents of the pack and other information

What DOMADOL contains:

The active substance is tramadol hydrochloride. In DOMADOL each ml of solution contains 50 and each 2ml of solution contains 100 mg of tramadol hydrochloride.

The other ingredients are Citric Acid Anhydrous, Sodium Citrate and Water for Injection.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine

10. DETAILS OF MANUFACTURER

Manufactured by:

Akums Drugs & Pharmaceuticals Ltd.

2,3,4 & 5, Sector-6B, I.I.E., SIDCUL, Haridwar – 249403, INDIA.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Mfg Lic No. 29/UA/SC/P-2007 issued on 09.04.2018

12. DATE OF REVISION

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/DOMADOL 50,100mg Injection/APR-20/01/PI