TRAMAL
INJECTION

DESCRIPTION
Sterile solution, clear, colorless, free of fibers and particles.

COMPOSITION
Each ml contains Tramadol hydrochloride 50 mg.

EXCIPIENTS
Sodium Acetate Trihydrate, Water For Injection.

MODE OF ACTION
Tramadol is a centrally acting opioid analgesic. It is a non-selective pure antagonist at, and opioid receptors with a higher affinity for the receptor. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release. Tramadol is well absorbed orally with an absolute bioavailability of 75%. Tramadol and its metabolites are excreted primarily in the urine with observed plasma half-lives of 6.3 and 7.4 hours for tramadol and M1 respectively.

INDICATION
Tramal® is indicated for the management of moderate to severe chronic pain and pain related to diagnostic procedure.

CONTRAINDICATIONS
Tramal® is contraindicated
- in hypersensitivity to the active substance or any of the excipients listed in section list of 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 (see section Interaction with other medicinal products and other forms of interaction),
- in patients with epilepsy not adequately controlled by treatment,
- for use in narcotic withdrawal treatment.

UNDESIRABLE EFFECTS
The most commonly reported adverse reactions are nausea and dizziness, both occurring in more than 10% of patients.
The frequencies are defined as follows:
Very common: 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.

Respiratory, thoracic and mediastinal disorders:
Rare: respiratory depression, dyspnea.
If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly (see section Interaction with other medicinal products and other forms of interaction), respiratory depression may occur.
Worsening of asthma has been reported, though a causal relationship has not been established.

Nervous system disorders:
Very common: dizziness.
Common: headache, somnolence.
Rare: speech disorders, paraesthesia, tremor, epileptiform convulsions, muscle contractions involuntary, coordination abnormal, syncope.
Convulsion occurred mainly after administration of high doses of tramadol or after concomitant treatment with medicinal products which can lower the seizure threshold. (see section Special warnings and precautions for use and Interaction with other medicinal products and other forms of interaction).

Psychiatric disorders:
Rare: hallucination, confusional state, 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 euphoric mood, occasionally dysphoria), changes in activity (usually suppression, occasionally increase) and changes in cognitive and sensorial capacity (e.g. decision behaviour, perception disorders). Drug dependence may occur. Symptoms of drug withdrawal syndrome, similar to those occurring during opiate withdrawal, may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms. Other symptoms that have very rarely been seen with tramadol discontinuation include: panic attacks, severe anxiety, hallucinations, paraesthesias, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalization, derealization, paranoia).

Eye disorders:
Rare: miosis, mydriasis, vision blurred.

Gastrointestinal disorders:
Very common: nausea.
Common: constipation, dry mouth, vomiting
Uncommon: retching, gastrointestinal discomfort (a feeling of pressure in the stomach, bloating), diarrhoea.

Skin and subcutaneous tissue disorders:
Common: hyperhidrosis.
Uncommon: dermal reactions (e.g. pruritus, rash, urticaria).

Musculoskeletal and connective tissue disorders:
Rare: motorial weakness.

Hepatobiliary disorders:
In a few isolated cases hepatic enzyme increased 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. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis.

General disorders and administration site conditions:
Common: fatigue.

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 other psychotropic substances, particularly alcohol.

Incompatibilities
Tramal® 50 mg/ml or 100 mg/2 ml solution for injection has proved to be incompatible (immiscible) with solutions for injection of diclofenac, indometacine, phenylbutazone, diazepam, flunitrazepam, midazolam, glyceryl trinitrate.

PRECAUTIONS
Tramal® may only be used after careful consideration of the benefit/risk ration and relevant precaution in:
- Dependence on opioids.
- Consciousness disorders of uncertain origin, shock.
- Disorders of the respiratory center or function.
- Increased intracranial pressure due to head injuries or brain diseases.

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

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 medication that lowers the seizure threshold (see “interaction”). Patients with epilepsy or those susceptible to seizures should be only treated with tramadol if there are compelling circumstances.

Tramadol has a low dependence potential. On long term use tolerance, psychic and physical dependence may develop. In patients with tendency to drug abuse or dependence, treatment with Tramal® supositoria should only be carried out for short periods under strict medical supervision.

Tramal® is not suitable as a substitute in opioid-dependent patients. Although tramadol is an opiate agonist, it cannot suppress morphine withdrawal symptoms.

Keterangan:

Black

Tramal® 50 solution for injection is not suitable for children below the age of 1 years.

During treatment with Tramal® 100 solution for injection, alcohol should be avoided as it may have an unfavorable influence on the effect of the drug.

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.

Tramadol - administered before or during birth - does not affect uterine contractility. In neonates it may induce changes in the respiratory rate which are usually not clinically relevant.

Chronic use during pregnancy may lead to neonatal withdrawal symptoms.

Breast-feeding

During lactation about 0.1% of the maternal dose is secreted into the milk. Tramadol is not recommended during breast-feeding. After a single administration of tramadol it is not usually necessary to interrupt breast-feeding.

Fertility

Post marketing surveillance does not suggest an effect of tramadol on fertility.

Animal studies did not show an effect of tramadol on fertility.

DRUG INTERACTIONS

Interaction with other medicinal products and other forms of interaction.

Tramadol should not be combined with MAO inhibitors (see section Contraindication).

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 Tramal®.

Concomitant administration of tramadol with other centrally depressant medicinal products including alcohol may potentiate the CNS effects (see section Undesirable effects).

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 antidepressants, antipsychotics and other seizure threshold-lowering medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.

Concomitant therapeutic use of tramadol and serotonergic drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see section **Contraindications**), 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 (see section Undesirable effects).

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.

APPLICATION AND DOSAGE

The dosage should be adjusted to the intensity of the pain and the sensitivity of the individual patient. Unless otherwise prescribed, Tramal® 50 solution for injection should be administered as follow:

Single dose for adults and adolescents over 12 years of age:

i.v. 1 - 2 ampoules (50 - 100 mg - injected slowly or diluted in solution for infusion and infused)

i.m. 1 - 2 ampoules (50 - 100 mg)

s.c. 1 - 2 ampoules (50 - 100 mg)

In generally the daily dose should not exceed 400 mg tramadol HCl (equivalent to 8 Tramal® 50 ampoules).

For the treatment of severe post-operative pain, on-demand pain relief may require even higher doses in the first few hours. In general, over 24 hours more than the normal doses are not necessary.

Children : In children from the age of one year, Tramal® 50 can be given in a dose of 1-2 mg/kg body weight (0.1 ml Tramal® 50 = 5 mg tramadol hydrochloride).

Geriatric patients : In acute pain a dosage adjustment is not necessary as Tramal® is given only once or a few times. In chronic pain a dosage adjustment is usually not necessary in elderly patients (up to 75 years) with no clinically manifest hepatic or renal insufficiency. In old patients (above the age of 75 years) elimination may be prolonged. Therefore, if necessary the dosage intervals are to be extended according to the patient's requirements.

Hepatic and renal insufficiency/dialysis : In acute pain a dosage adjustment is not necessary as Tramal® is given only once or a few times. In patients with severe renal and/or hepatic insufficiency. Tramal® should not be administered. In less severe cases prolongation of the dosage interval should be considered.

Duration of treatment : Tramal® must not be given for longer than therapeutically absolutely necessary. If long-term pain treatment is necessary, checks should be carried out at regular and brief intervals (if necessary with breaks in treatment) as to whether and in what doses further treatment with Tramal® is necessary.

Over dosage

Symptoms : In principle, on intoxication with tramadol symptoms similar to those of other centrally acting analgesics (opioids) are to be expected, in particular miosis, vomitting, cardiovascular collapse, reduced level of consciousness up to coma, convulsions and respiratory arrest.

Treatment : The general emergency measures to keep open the respiratory tract (aspiration!), maintenance of the respiration and circulation depending on the symptoms apply. An antidote for respiratory depression is naloxone. In animal studies naloxone had no effect on convulsions. In such cases diazepam should be given i.v.

Tramadol is only minimally eliminated from the serum by dialysis. Therefore treatment of acute intoxication with Tramal® with haemodialysis or haemofiltration alone is not suitable.

Information for the Patient :

Tramal® is a potent medicinal product for the relief of pain, e.g. in wound pain, fractures, severe nerve pain, tumour pain, heart attack. It should not be used for minor pain. The effect sets in quickly and lasts for some hours.

PRESENTATIONS

Tramal® 50 Injection
Box of 5 ampoules @ 1 ml
Reg. No. DKL1421644043B1

Tramal® 100 Injection
Box of 5 ampoules @ 2 ml
Reg. No. DKL1421644043A1

ON MEDICAL PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

Keep out of reach of children
Store below 30°C

Manufactured by :
PT. Prima Medika Laboratories
Tangerang - Indonesia

For :

PHAROS
Jakarta - Indonesia

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