TRAPADOL INJECTION

FOR I.V./I.M. USE ONLY

Composition :

Each 2ml. contains :

Tramadol Hydrochloride I.P. 100mg.

Water for injection I.P. q.s.

CLINICAL PHARMACOLOGY :

Pharmacodynamics

Tramadol is a centrally acting synthetic opioid analgesic structurally related to codeine and morphine; consist of two enantiomers, both of which contribute to analgesic activity through different mechanisms. Although its mode of action is not completely understood.

Tramadol and the metabolite O-desmethyl – tramadol are agonist of the μ-opioid receptors. Tramadol inhibits serotonin reuptake and O- desmethyl tramadol norepinephrine reuptake, enhancing inhibitory effects on pain transmission in the spinal cord. The synergistic actions of the two enantiomers of tramadol improve the analgesic efficacy and tolerability of this drug.

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. Effect on the cardiovascular system tend to be slight.

Molecular formula of tramadol is $C_{16}H_{25}NO_2$ •HCl

Pharmacokinetics :

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 subjects .Tramadol undergoes hepatic metabolism with approximately 85% of an intravenous dose being metabolised in young healthy volunteers. Tramadol is biotransformed primarily by N- and O-demethylation and by glucuronidation of the O-demethylation products. Eleven metabolites have so far been identified in man. Only one metabolite, O-demethyl tramadol (M1), is pharmacologically active showing analgesic activity. 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.

Characteristics in patients:

Effect of age: Tramadol pharmacokinetics show little age-dependence in patients up to the age of 75 years. In patients 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 Odesmethyl 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.

THERAPEUTIC INDICATIONS :

For the treatment and prevention of moderate to severe pain.

DOSES AND METHOD OF ADMINISTRATION **:**

The injection is for parenteral administration either intramuscularly or by slow intravenous injection. As with all analgesic drugs the dosing of Tramadol Injection should be adjusted depending on the severity of the pain and the individual clinical response of the patient.

Adults: A single dose of 50 or 100 mg 4-6 hourly is usually required. Intravenous injections must be given slowly over 2-3 minutes. For severe (post-operative) pain, administer an initial bolus of 100 mg. during the 60 minutes following the initial bolus, further doses of 50 mg may be given every 10-20 minutes, up to a total dose of 250 mg including the initial bolus. Subsequent doses should be 50 or 100 mg administered 4-6 hourly. The dose should not be doubled if any dose has forgotten. Administration should be continued as before. A total daily dose of 400 mg should not be exceeded except in special clinical circumstances.

Elderly patients: Dosing as for adults but it should be noted that in a study in elderly patients (aged over 75 years) the elimination half-life for orally administered tramadol was increased by 17%.

Patients with renal insufficiency/renal dialysis: As the elimination of tramadol may be prolonged in patients with renal impairment, the usual initial adult doses should be employed, but prolongation of the dosage interval should be carefully considered according to the patient's requirements.

For creatinine clearance less than 30 ml/min the dosing should be increased to 12 hourly intervals. For creatinine clearance less than 10 ml/min (severe renal impairment) tramadol is not recommended.

Patients with hepatic insufficiency: It should be noted that as the elimination of tramadol may be prolonged in severe hepatic impairment, although the usual initial adult doses should be used, prolongation of the dosing should be at 12 hourly intervals. Children:

Over 14 years: Dosage as for adults.

Children aged 1 to 14 years : Receive 1-2 mg tramadol hydrochloride per kg body weight as a single dose.

CONTRAINDICATIONS :

Tramadol 50mg/ml Solution for Injection should not be given to patients who have previously demonstrated hypersensitivity towards tramadol or any of the other ingredients and 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 50mg/ml Solution for Injection is contraindicated in patients with epilepsy not adequately controlled by treatment.
Tramadol must not be used in narcotic withdrawal treatment.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Warnings

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

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 50mg/ml Solution for Injection is not a suitable substitute in opioid dependent patients. The product does not suppress morphine withdrawal symptoms although it is an opioid agonist.
This drug 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 50mg/ml Solution for Injection 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.
Its use during potentially very light planes of general anaesthesia should be avoided.

INTERACTION WITH OTHER DRUGS :

Tramadol 50mg/ml Solution for Injection should not be combined with Monoamine oxidase inhibitor (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.
The combination with mixed agonist/antagonists (e.g. buprenorphine, nalbuphine, pentazocine) and tramadol is not advisable, because the analgesic effect of a pure agonist may be theoretically reduced in such circumstances.
Concomitant administration of Tramadol 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.

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.

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 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 should not be administered during breast-feeding. After a single administration of tramadol however, it is not usually necessary to interrupt breast feeding.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES :

Tramadol 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.

UNDISERABLE 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.

Cardiovascular system disorders:
Uncommon: Cardiovascular regulation like palpitation, tachycardia, postural hypotension or cardiovascular may occur. 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.

Eye disorders:
Rarely may occur blurred vision

Respiratory system disorders:
Rarely may occur dyspnoea.
Worsening of asthma has been reported, though a causal relationship has not been established.

Gastrointestinal disorders:
Very commonly may occur nausea and commonly vomiting, constipation, dry mouth.

Skin and subcutaneous disorders:
Commonly patient may suffer sweating.

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 meiosis, 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 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 haemo-filtration alone is not suitable for detoxification.

INCOMPATIBILITIES :

Precipitation will occur if Tramadol 50mg/ml Solution for Injection is mixed in the same syringe with injections of diazepam, diclofenac sodium, indomethacin, midazolam and piroxicam.
Tramadol Injection must not be mixed with other medicinal products except with 4.2% sodium bicarbonate and Ringer's solution(compatible for up to 24 hours) or with 0.9% sodium chloride ,
0.18% sodium chloride and 4% glucose, sodium lactate compound, 5% glucose (compatible for up to 5days).

STORAGE CONDITION: Store below 25ºC.

PRESENTATION : 5 X 2ml. ampoules in a tray with outer box .