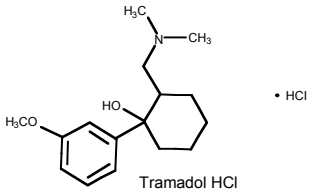
Pantra™
[Tramadol HCl]

پینٹرا

Capsules 50mg
Injection 100mg/2mL

DESCRIPTION
Pantra (Tramadol HCl) is a centrally acting opioid analgesic. It also has noradrenergic and serotonergic properties that may contribute to its analgesic activity. Chemically, it is (±)-cis-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. Its molecular formula is $C_{16}H_{25}NO_2 \cdot HCl$ and the structural formula is:



Tramadol HCl

QUALITATIVE AND QUANTITATIVE COMPOSITION
Pantra (Tramadol HCl) is available for administration as:

Pantra Capsules 50mg
Each capsule contains:
Tramadol HCl USP … 50mg

Pantra Injection 100mg/2mL
Each 2mL contains:
Tramadol HCl USP … 100mg

CLINICAL PHARMACOLOGY
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.

Pharmacokinetics
Absorption
Tramadol is readily absorbed after oral doses but is subject to some first-pass metabolism. Mean absolute bioavailability is about 70 to 75% after oral and 100% after intramuscular injection.

Distribution
Tramadol has a high tissue affinity with an apparent volume of distribution of 306 liters after oral administration and 203 liters after intravenous administration respectively.
The distribution of tramadol after an intravenous administration is rapid and is biphasic with different half-lives of 0.31 ± 0.17hours which is the initial rapid phase and 1.7 ± 0.4hours which is the slower phase respectively. After intravenous administration of 100mg tramadol, the serum concentration was 613 ± 221ng/mL at 15 minutes post dosing and 409 ± 79ng/mL at 2 hours post dosing.

Metabolism
Tramadol undergoes hepatic metabolism with approximately 85% of an oral and intravenous dose. Tramadol is metabolised by N and O-desmethylation via the cytochrome P450 isoenzymes CYP3A4 and CYP2D6 and glucuronidation or sulfation in the liver. The metabolite O-desmethyltramadol is pharmacologically active.

Elimination
Tramadol is essentially excreted via the kidneys. The mean elimination half-life of tramadol following oral and intravenous administration is 5 - 6 hours. Approximately 90% of an oral dose is excreted by the kidneys. Total clearance of tramadol was 28.0L/h following intravenous administration.

Special Population
Effect of age
In elderly patients aged over 75 years, the terminal elimination half-life was 7.0 ± 1.6 hours compared to 6.0 ± 1.5 hours in adults after oral administration.

Hepatic or Renal impairment
The terminal half-life of elimination ($t_{1/2}$) of tramadol may be prolonged in patients with hepatic or renal dysfunction. In liver cirrhosis patients, the mean $t_{1/2}$ of tramadol was 13.3 ± 4.9 hours. In patients with renal failure (creatinine clearance < 5 mL/min) the $t_{1/2}$ of tramadol was 11.0 ± 3.2 hours and that of O-desmethyltramadol was 16.9 ± 3.0 hours.

THERAPEUTIC INDICATIONS
Pantra (Tramadol HCl) is indicated for the treatment of moderate to severe pain.

DOSAGE AND ADMINISTRATION
The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient. Generally, the lowest effective dose for analgesia should be selected.

Oral
Adults
For acute pain:
An initial dose of 100mg is usually necessary. This can be followed by doses of 50mg or 100mg not more frequently than 4 hourly.

For pain associated with chronic conditions:
Use in an initial dose of 50mg and then titrate dose according to pain severity. The need for continued treatment should be assessed at regular intervals as withdrawal symptoms and dependence rarely occurs.

A total oral daily dose of 400mg should not be exceeded except in special clinical circumstances.

Parenteral
Pantra (Tramadol HCl) Injection 100mg/2mL should be administered as follows:

Adults
Pantra (Tramadol HCl) Injection may be administered intramuscularly, by slow intravenous injection, or diluted in solution for administration by infusion.
The usual dose is 50mg 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 600mg. A total parenteral daily dose of over 600mg should not be exceeded except in special circumstances.

Pantra (Tramadol HCl) Injection is compatible for up to 24 hours with Water for Injection (WFI), Sodium Chloride Solution for Injection 0.9% and Glucose Solution for Injection 5%. The prepared infusion solution should be made immediately before use.

Special Population
Children
Over 12 years: Dosage of Pantra (Tramadol HCl) for children over 12 years is same as for adults.
Under 12 years: Pantra (Tramadol HCl) is not recommended for children under 12 years.

Elderly patients
A dose adjustment is not usually necessary in 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 impairment
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.
- For creatinine clearance <30 ml/min the dosing should be increased to 12 hourly intervals.
- For creatinine clearance <10 ml/min (severe renal impairment) tramadol is not recommended.

Tramadol is removed very slowly by hemodialysis or hemofiltration and therefore post-dialysis dosing to maintain analgesia is usually unnecessary.

Duration of treatment
Pantra (Tramadol HCl) should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with Pantra (Tramadol HCl) 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.

ADVERSE REACTIONS
Very common: Dizziness, vomiting and nausea.
Common: Headache, drowsiness, constipation, dry mouth, sweating and fatigue.
Uncommon: Effects on cardiovascular regulation (palpitation, tachycardia, postural hypotension or cardiovascular collapse), retching, gastrointestinal irritation (a feeling of pressure in the stomach, bloating) and dermal reactions (e.g. pruritus, rash, urticaria).

CONTRAINDICATIONS
Tramadol HCl is contraindicated in:
- Patients with known hypersensitivity to tramadol HCl or to any excipient of the product.

- Patients suffering from acute intoxication with hypnotics, centrally acting analgesics, opioids, psychotropic drugs or alcohol.
- Patients who are receiving monoamine oxidase (MAO) inhibitors or who have taken them within the last 14 days.
- Patients suffering from uncontrolled epilepsy.
- Narcotic withdrawal treatment.

PRECAUTIONS
- Tramadol has a low dependence potential. On long-term use tolerance, psychic and physical dependence may develop.
- Convulsions have been reported at therapeutic doses and the risk may be increased at doses exceeding the usual upper daily dose limit.
- Tramadol HCl should be used with prudence in patients who have shown previous hypersensitivity to opiates, and in patients with severe renal or hepatic impairment, head injury, decreased level of consciousness, increased intracranial pressure, or patients in shock or at risk of convulsions.
- In patients sensitive to opiates, tramadol HCl should only be used with caution.
- Care should be taken when administering tramadol HCl to patients with existing respiratory depression or excessive bronchial secretion and in those patients taking concomitant CNS depressant drugs.

Pregnancy
There is inadequate evidence available on the safety of tramadol in human pregnancy. Therefore, tramadol HCl should not be used in pregnant women.

Nursing Mothers
Tramadol HCl should not be administered during breast feeding as tramadol and its metabolites have been detected in breast milk. 0.1% of the dose administered to the mother may be excreted in milk.

Drug Interactions
- Tramadol may potentiate the CNS depressant effects of other centrally acting drugs (including alcohol) when administered concomitantly with such drugs.
- Tramadol can induce convulsions and increase the potential for selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, anti-psychotics and other seizure threshold lowering medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.
- Administration of tramadol HCl together with carbamazepine results in markedly decreased serum concentrations of tramadol which may reduce analgesic effectiveness and shorten the duration of action.
- Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (e.g. warfarin) due to increased INR and ecchymoses in some patients.

OVERDOSAGE
Symptoms
Symptoms of tramadol overdose include vomiting, miosis, sedation, seizures, respiratory depression and hypotension, with circulatory failure and coma. Respiratory failure may also occur. Such symptoms are typical of opioid analgesics.

Treatment
Treatment of overdose requires the maintenance of the airway and cardiovascular functions. Respiratory depression may be reversed using naloxone and fits controlled with diazepam. The treatment of acute overdose of tramadol using hemodialysis or hemofiltration alone is not sufficient or suitable due to the slow elimination of tramadol from the serum by these routes.

STORAGE
Pantra (Tramadol HCl) Capsules 50mg
Store at 25°C (Excursions permitted between 15°C - 30°C).
Protect from sunlight and moisture.

Pantra (Tramadol HCl) Injection 100mg/2mL
Store at 25°C (Excursions permitted between 15°C - 30°C).
Protect from heat and light.
Do not freeze.

HOW SUPPLIED
Pantra (Tramadol HCl) Capsules 50mg are available in pack of 10's.
Pantra (Tramadol HCl) Injection 100mg/2mL are available in pack of 5's.

Keep out of reach of children

To be sold on prescription of a registered medical practitioner only

The expiration date refers to the product correctly stored at the required conditions.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
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