routes.

STORAGE
Store between 15 to 30° C in a dry place, protect from light. To be dispensed on the prescription of a registered medical practitioner only.
Keep out of the reach of children.

HOW SUPPLIED
Plagesic Tablets 50mg are available in pack of 10's.
Plagesic-SR Tablets 100 mg are available in pack of 10's.
Plagesic-*P* Tablets 37.5 mg + 325 mg available in pack of 10's.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
دوا کو ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان خشک جگہ پر رکھیں، روشنی سے بچائیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے پر فروخت کریں۔ بچّوں کی پہنچ سے دور رکھیں۔

Manufactured by:
Platinum Pharmaceuticals (Pvt) Ltd.
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Mfg. Lic No. 000415

QAR No. AW23-1166

Plagesic Tablets پلاجیسک

DESCRIPTION
Plagesic 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 C16H25NO2.HCl.

The molecular weight of Paracetamol is 151.17. Paracetamol is an analgesic and antipyretic agent Tramadol and Paracetamol combination is used to relieve pain. When used together, the combination provides better pain relief than either medicine used alone. In some cases, you may get relief with lower doses of each medicine.

QUALITATIVE AND QUANTITATIVE COMPOSITION
Plagesic is available for administration as:

Plagesic Tablets 50 mg
Each tablet contains:
Tramadol HCl... 50 mg
Product Complies U.S.P. Specs.

Plagesic-SR Tablets 100 mg
Each tablet contains:
Tramadol HCl... 100 mg
Product Complies U.S.P. Specs.

Plagesic-P Tablets 37.5 mg + 325 mg
Each tablet contains:
Tramadol HCl... 37.5 mg
Paracetamol..... 325 mg
Product Complies U.S.P. Specs.

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 firstpass metabolism.

Distribution
Plagesic has a high tissue affinity with an apparent volume of distribution of 306 liters after oral administration.

Peak Plasma Concentration:
Plagesic Tablets: After oral administration of 100mg tramadol hydrochloride the peak plasma concentration is reached after 2 hours.
Plagesic-SR Tablets: After oral administration of 100mg tramadol hydrochloride the peak plasma concentration is reached after 4.9 hours.
Plagesic-P gives a peak plasma concentration of paracetamol within one hour and is not affected by Co-administration with tramadol.

Metabolism
Tramadol undergoes hepatic metabolism with approximately 85% of an oral and intravenous dose. Tramadol is metabolised by N and Odesmethylation via the cytochrome P450

isoenzymes CYP3A4 and CYP2D6 and glucuronidation or sulfation in the liver. The metabolite Odesmethyltramadol 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 (t1/2) of tramadol may be prolonged in patients with hepatic or renal dysfunction. In liver cirrhosis patients, the mean t1/2 of tramadol was 13.3 ± 4.9 hours. In patients with renal failure (creatinine clearance < 5 mL/min) the t1/2 of tramadol was 11.0 ± 3.2 hours and that of O-desmethyltramadol was 16.9 ± 3.0 hours.

THERAPEUTIC INDICATIONS
Plagesic (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.

Special Population
Children
Over 12 years: Dosage of Plagesic (Tramadol HCl) for children over 12 years is same as for adults.
Under 12 years: Plagesic (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.

Plagesic-SR Tablets: In case of severe renal and/or severe hepatic insufficiency Plagesic-SR prolonged release tablets are not recommended.

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

Use with other Paracetamol-containing Products
Due to the potential for paracetamol hepatotoxity at doses higher than the recommended dose, Plagesic-P should not be used concomitantly with other Paracetamol containing products.

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 eliminat ion of tramadol from the serum by these