TRAMADOL HYDROCHLORIDE TABLETS
Rx only
1000 Tablets

Each tablet contains:
Tramadol Hydrochloride.................. 50 mg

Usual Dosage: See attached labeling for complete prescribing information.

Dispense in a tight container.

Manufactured by: CorePharma LLC
Middlesex, NJ 08846

MF# 151

Tramadol Hydrochloride

DESCRIPTION
Tramadol hydrochloride is a centrally acting analgesic. It is a synthetic analog of codeine and its action is unknown. Tramadol hydrochloride is available for oral administration as tramadol hydrochloride tablets 50 mg. In addition, it is also contains the following inactive ingredients: cornstarch, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and zinc stearate.

CLINICAL PHARMACOLOGY

Pharmacokinetics
Tramadol hydrochloride is a centrally acting synthetic opioid analgesic. Although its mode of action is not completely understood, tramadol is at least two complementary mechanisms appear to be responsible for its analgesic effects: (1) blockade of norepinephrine and serotonin reuptake, and (2) activation of opioid activity.

Pharmacodynamics
Tramadol hydrochloride has been shown to inhibit ventricular and atrial arrhythmias in vitro and in vivo. It has a potent analgesic effect. 

Absorption:
Tramadol is rapidly and almost completely absorbed after oral administration. The mean absolute bioavailability of a 100 mg dose is 75%.

Steady-State Plasma Concentrations of both tramadol and \( \text{M} \) are achieved within 5 days with 0.2 mg/kg.

**Figure 1:** Mean (±SD) Plots for Steady-State Plasma Concentrations after a Single 100 mg Oral Dose

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>tramadol</th>
<th>( \text{M} )</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>50</td>
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<td>1</td>
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<td>5</td>
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**Figure 2:** Mean (±SD) Plots for Steady-State Plasma Concentrations after a Multiple 100 mg Oral Dose

<table>
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</tbody>
</table>

**Figure 3:** Mean (±SD) Plots for Steady-State Plasma Concentrations after a Single 100 mg Oral Dose and Twenty-Nine 100 mg Oral Doses of Tramadol 24 h

**Figure 4:** Mean (±SD) Plots for Steady-State Plasma Concentrations after a Single 100 mg Oral Dose and Twenty-Nine 100 mg Oral Doses of Tramadol 24 h

**Figure 5:** Mean (±SD) Plots for Steady-State Plasma Concentrations after a Single 100 mg Oral Dose and Twenty-Nine 100 mg Oral Doses of Tramadol 24 h

**Figure 6:** Mean (±SD) Plots for Steady-State Plasma Concentrations after a Single 100 mg Oral Dose and Twenty-Nine 100 mg Oral Doses of Tramadol 24 h

**Figure 7:** Mean (±SD) Plots for Steady-State Plasma Concentrations after a Single 100 mg Oral Dose and Twenty-Nine 100 mg Oral Doses of Tramadol 24 h
The molecular formula of tramadol hydrochloride is C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>·HCl and its molecular weight is 239.7.

Tramadol hydrochloride is a white, bitter, crystalline, odorless powder. It is freely soluble in water and slightly soluble in alcohol (1:1, 1:5). The aqueous solution has a pH of 4.7.

The analgesic effect of tramadol hydrochloride is characterized by a relatively long onset time and a long duration of action. It is rapidly absorbed from the gastrointestinal tract, with peak plasma concentrations occurring within 1-2 hours. Tramadol is extensively metabolized in the liver and the main metabolites are O-desmethyltramadol and N-demethyltramadol. The plasma elimination half-life is approximately 6 hours.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Tramadol hydrochloride is a centrally acting, synthetic opioid analgesic. It is a weak agonist of the mu and kappa opioid receptors, with a lower affinity for the delta receptor. Its analgesic effect is thought to be mediated by the inhibition of the reuptake of serotonin and norepinephrine. This dual mechanism of action contributes to its analgesic efficacy.

Pharmacokinetics

Tramadol is rapidly absorbed after oral administration, with peak plasma concentrations occurring within 1-3 hours. It is extensively metabolized in the liver, with two main metabolites: O-desmethyltramadol and N-demethyltramadol. The plasma elimination half-life is approximately 6 hours.

Indications

Tramadol hydrochloride is indicated for the management of moderate to severe pain.

Contraindications

Tramadol hydrochloride is contraindicated in patients with a history of a hypersensitivity reaction to tramadol or its metabolites, in patients with a history of drug or alcohol abuse, and in patients with renal or hepatic impairment.

Warnings

Tramadol hydrochloride can cause drowsiness, dizziness, and confusion, especially in elderly patients. It should be used with caution in patients with a history of depression or other mental health disorders.

Drug Interactions

Tramadol hydrochloride can interact with other drugs that affect the central nervous system, such as opioids, sedatives, and antidepressants.

Overdose

In case of overdose, supportive and symptomatic treatment should be provided. Gastric lavage, oxygen administration, and mechanical ventilation may be necessary. Activated charcoal may be administered to prevent further absorption of the drug.

Dosage

The recommended initial dose of tramadol is 50 mg orally every 6-8 hours. The dose may be increased based on the patient's response and tolerance.

Special Populations

Elderly patients may require a lower initial dose due to reduced hepatic metabolism. Patients with hepatic or renal impairment may require a lower initial dose or dosing interval.

Pregnancy

Pregnant women should be monitored closely during labor and delivery. The use of tramadol during pregnancy has not been studied in detail in pregnant women, but it is generally considered safe if used at appropriate doses.

Lactation

Tramadol is excreted in breast milk. Mothers should consult with their healthcare provider before breastfeeding.

Adverse Reactions

Common adverse reactions include drowsiness, dizziness, confusion, and nausea.

References

- United States National Library of Medicine, Drugs@FDA
- FDA, Drug Approval Applications
- FDA, Adverse Event Reporting System

Graph: Graph of the plasma concentration-time curve for tramadol and its metabolites.

Figure 3: Graph showing the plasma concentration-time curve for tramadol (solid line) and O-desmethyltramadol (dashed line) after a single oral dose of 100 mg of tramadol hydrochloride.

Table 1: Summary of tramadol hydrochloride dosage recommendations.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Tramadol Dose</th>
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<tbody>
<tr>
<td>Moderate pain</td>
<td>100 mg/day</td>
</tr>
<tr>
<td>Severe pain</td>
<td>200 mg/day</td>
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</tbody>
</table>

Note: The information provided is for educational purposes only and should not replace professional medical advice.
Table 1

| Pharmacokinetics Parameters for Transdermal Naltrexone and Naltrexone Hydrochloride |
|-----------------|-------------------|--------------------------|-----------------|-----------------|
| **Population**  | **Drug** | **Peak Concentration** | **Time to Peak** | **Clearance** |
| Healthy Adults | Transdermal | 6.2 (5.8) | 3.3 (2.7) | 1.0 (0.8) |
| M1 | 110 (120) | 2.4 (1.8) | 2.5 (2.0) |
| M2 | 76 (63) | 0.6 (0.5) | 0.6 (0.5) |
| Healthy Adults | Oral Naltrexone | 1.5 (1.2) | 0.7 (0.3) | 0.8 (0.5) |
| M1 | 65 (60) | 2.0 (1.6) | 2.1 (1.6) |
| M2 | 38 (30) | 1.1 (0.9) | 1.0 (0.8) |
| U.S. 240 mg | Transdermal | 2.7 (2.4) | 3.1 (2.6) | 2.7 (2.2) |
| M1 | 28 (14) | 2.1 (1.7) | 2.1 (1.7) |
| M2 | 18 (10) | 1.0 (0.8) | 1.0 (0.8) |
| Oral Naltrexone | 300 mg | Oral Naltrexone | 120 mg |
| M1 | 27 (11) | 2.0 (2.0) | 2.0 (2.0) |
| M2 | 15 (4) | 1.0 (0.8) | 1.0 (0.8) |
| U.S. 100 mg | Transdermal | 1.0 (0.8) | 1.0 (0.8) | 1.0 (0.8) |
| M1 | 15 (11) | 0.8 (0.6) | 0.8 (0.6) |
| M2 | 10 (5) | 0.7 (0.5) | 0.7 (0.5) |
| Oral Naltrexone | M1 | 10 (5) | 0.7 (0.5) | 0.7 (0.5) |
| Oral Naltrexone | M2 | 10 (5) | 0.7 (0.5) | 0.7 (0.5) |
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| M1 | 27 (11) | 2.0 (2.0) | 2.0 (2.0) |
| M2 | 15 (4) | 1.0 (0.8) | 1.0 (0.8) |

**a** SD = Single dose; MD = Multiple dose; p.o. = Oral administration; i.v. = intravenous administration.

**b** Represents the oral bioavailability of naltrexone.

**c** Not applicable

**d** Not measured

**Notes:** Oral administration of transdermal hydrochloride with food does not significantly affect its rate or extent of absorption, therefore hydrochloride can be administered without regard to food.

**Distribution:**

The volume of distribution of naltrexone is 2.6 and 2.9 liter/kg in male and female subjects, respectively, following a 10 mg intravenous dose. The binding to plasma in human plasma protein is approximately 20% and binding also appears to be independent of concentration up to 10 mg/L. Elimination of plasma levels following occurs only at concentrations outside the clinically relevant range.

**Ametabolism:**

Naltrexone is extensively metabolized after oral administration. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 70% of the dose is excreted as metabolites. The major metabolic pathways appear to be the 17-epimerization and glucuronidation of naltrexone in the liver. The metabolite (O-desmethyltransdermal Naltrexone) is pharmacologically active in animal models.

Approximately 14.9% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome

**INDICATIONS AND USAGE:**

*Transdermal Naltrexone* tablets are indicated for the management of moderate to severe pain in adults.

**CONTRAINDICATIONS:**

*Transdermal Naltrexone* should not be administered to patients who have previously demonstrated hypersensitivity to transdermal or any other component of the product or excipient. Transdermal hydrochloride is not indicated for the treatment of opioid addiction where opioids are contraindicated, including acute intoxication with any of the following: chronic hypoxia, narcotic, centrally acting anesthetics, opioids or psychotropic drugs. Continued use of naltrexone hydrochloride may worsen central nervous system and respiratory depression in these patients.

**WARNINGS:**

*Serious Risk:*

Serious and life-threatening reactions have been reported in patients receiving transdermal hydrochloride within the recommended dosage range. Such reactions post-marketing require careful that suicide risk is increased in patients treated with transdermal hydrochloride above the recommended range. Continued use of naltrexone hydrochloride increases the suicide risk in patients taking:

- Self-poisoning
- Suicide
- Interaction with benzodiazepines or tricyclic antidepressants
- Antidepressants, opioids, or other psychotropic drugs

Administration of transdermal hydrochloride may enhance the suicide risk in patients taking:

- Benzodiazepines (see above WARNINGS - Use with MAO inhibitors)
- Other drugs that reduce the seizure threshold
- Alcohol
- other substances that increase the risk of suicide

**Risk of convulsions may also increase in patients with substance abuse problems.**

**Respiratory Depression:**

Decreased intercostal pressure or spinal nerve block: Naltrexone hydrochloride should be used with caution in patients with impaired respiratory function, including chronic obstructive pulmonary disease, COPD, and other respiratory conditions. Increased intercostal pressure or spinal nerve block: Naltrexone hydrochloride may increase the risk of respiratory depression in these patients.

**Increased Intracranial Pressure or Head Trauma:**

Naltrexone hydrochloride should be used with caution in patients with increased intracranial pressure or head trauma. For patients with chronic obstructive pulmonary disease, patients with marked intracranial pressure, or patients with head trauma, prolonged administration of transdermal hydrochloride may potentiate the risk of respiratory depression.

**Use in The Elderly:**

Naltrexone hydrochloride may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

**Use in Children:**

Naltrexone hydrochloride tablets are not indicated for children.
Use with MAO inhibitors and selective serotonin reuptake inhibitors

Use tranylcypromine with great caution in patients taking monoamine oxidase inhibitors. Animal studies have shown tranylcypromine to be associated with cardiotoxicity. Concurrent use of tranylcypromine with MAO inhibitors or SSRIs is contraindicated for the risk of adverse events, including arrhythmia and serotonin syndrome. Withdrawal

Withdrawal symptoms may occur if tranylcypromine is taken abruptly. (See DRUG ABUSE, AND DEPENDENCE.) These symptoms may include anxiety, sweating, tetanic spasm, nausea, vomiting, tinnitus, visual disturbances, autonomic dysfunction, and weak hyper flexion. Clinical experience suggests that withdrawal symptoms may be relieved by increasing the medication.

Physical Dependence and Abuse

Tranylcypromine has potential systemic and physical dependence of the monoamine type (Table

Use tranylcypromine with caution in patients with a history of drug dependency. Patients should be informed of the potential for drug dependence. Use in Renal and Hepatic Disease

Impaired renal function results in a decreased rate and extent of excretion of tranylcypromine and its active metabolite, 5-HT. In patients with creatinine clearances of less than 30 mL/min, drug elimination is reduced (see DOSAGE AND ADMINISTRATION).

Patients with normal renal function should be instructed that the drug should be given with caution since the drug is eliminated through the kidney. With impaired renal function, the half-life of the drug is increased, so that it may take several days for the drug to be eliminated.

Information for Patients

Tranylcypromine tablets may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Tranylcypromine tablets may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Tranylcypromine tablets should be used with caution while using medications such as tricyclic antidepressants or other agents known to cause extrapyramidal reactions. The patient should be instructed to inform the physician if they become pregnant, or if they are planning to become pregnant (see PRECAUTIONS). Labor and Delivery. Tranylcypromine tablets should be used with caution in patients with a history of drug dependency. Patients should be instructed that the drug should be given with caution since the drug is eliminated through the kidney. With impaired renal function, the half-life of the drug is increased, so that it may take several days for the drug to be eliminated.

Drug Interactions

In vitro studies indicate that tranylcypromine is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when tranylcypromine is administered concurrently at therapeutic doses. Interactions do not appear to influence the metabolism of other drugs, since extensive phase I metabolism has been observed in human liver microsomes in vitro. Tranylcypromine tablets may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Tranylcypromine tablets should be used with caution while using medications such as tricyclic antidepressants or other agents known to cause extrapyramidal reactions. The patient should be instructed to inform the physician if they become pregnant, or if they are planning to become pregnant (see PRECAUTIONS). Labor and Delivery. Tranylcypromine tablets should be used with caution in patients with a history of drug dependency. Patients should be instructed that the drug should be given with caution since the drug is eliminated through the kidney. With impaired renal function, the half-life of the drug is increased, so that it may take several days for the drug to be eliminated.

Use with Daytime

Tranylcypromine tablets are contraindicated in patients with a history of drug dependency. Patients should be instructed that the drug should be given with caution since the drug is eliminated through the kidney. With impaired renal function, the half-life of the drug is increased, so that it may take several days for the drug to be eliminated.

Use with Celebrex

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**Cardiovascular, Respiratory, and Miscellaneous Effects**

- **Nausea, Respiratory, and Miscellaneous Effects:** Pregnancy Category C.
- **Drug Interactions:** In combination with trandolapril should be avoided due to potential increased risk of hyperkalemia.
- **Hypokalemia:** Potentially increased with trandolapril.
- **Potassium-Sparing Diuretics:** Potentially increased with trandolapril.

**Postmarketing Observations**

- **Pregnancy and Lactation:** Not recommended for use in pregnant women or in nursing women.
- **Hypertension:** Potentially increased with trandolapril.
- **Myocardial Infarction:** Potentially increased with trandolapril.

**Drug Interactions:**

- **Cyclosporine:** Potential for increased risk of myelosuppression.
- **Digoxin:** Potential for increased risk of hyperkalemia.
- **Lithium:** Potential for increased risk of hyperkalemia.
- **Potassium-Sparing Diuretics:** Potential for increased risk of hyperkalemia.

**Contraindications:**

- **Myocardial Infarction:** Potentially increased with trandolapril.
- **Hypertension:** Potentially increased with trandolapril.

**General Dose Selection**

- **Adults:** For patients with normal renal function, the usual dose is 1 mg once daily. For patients with decreased renal function, the dose may be titrated based on renal function. For patients with severe renal impairment (eGFR <30 ml/min), the dose should be reduced to 0.5 mg once daily.

**Pharmacology:**

- **Pharmacokinetics:** Absorption is rapid and complete. The peak plasma concentration is reached within 1-2 hours. The elimination half-life is approximately 14 hours.

**Clinical Studies:**

- **Hypertension:** In clinical trials, trandolapril was effective in lowering blood pressure in both normotensive and hypertensive patients. The dose-response relationship was linear for both blood pressure and renal function.

**Adverse Events:**

- **Hypotension:** Potentially increased with trandolapril.
- **Hyperkalemia:** Potentially increased with trandolapril.

**Precautions:**

- **Hypotension:** Potentially increased with trandolapril.
- **Hyperkalemia:** Potentially increased with trandolapril.

**Monitoring:**

- **Hypotension:** Monitor blood pressure and heart rate.
- **Hyperkalemia:** Monitor serum potassium levels.

**Overdosage:**

- **Symptoms:** Potentially increased with trandolapril.
- **Treatment:** Potentially increased with trandolapril.

**Additional Information:**

- **Cardiovascular, Respiratory, and Miscellaneous Effects:** Potential for increased risk of hypotension, hyperkalemia, and myelosuppression.
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