Doxepin hydrochloride is one of a class of psychotherapeutic agents known as dibenzoxepin tricyclic compounds. The molecular formula of doxepin HCl is C₂₇H₂₄ClNO₂ and its molecular weight is 315.84. It is a white crystalline solid readily soluble in water, lower alcohols and chloroform. Its structural formula is: \[
\text{MW: 315.84 (as HCl salt)}
\]

**CONTRAINDICATIONS**

Doxepin HCl is contraindicated in individuals who have shown hypersensitivity to the drug. Cross-sensitivity with other TCAs is possible. Patients with a known history of allergic reactions to other antidepressants or other antihistamines in a child, adolescent, or young adult must be closely observed during the initial treatment. Such patients must be warned about the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults. The occurrence of suicidal thoughts or behavior in children, adolescents, and young adults during treatment or after discontinuation of antidepressants, especially those with fluoxetine, has been noted. Furthermore, those who have attempted suicide or who are at risk for it are more likely to benefit from antidepressants. Patients with a history of drug or alcohol dependence or abuse must be closely observed during the initial treatment. Use of antidepressants in pediatric patients: Doxepin HCl is contraindicated in children under 12 years of age. The safety and effectiveness of doxepin HCl in children under 12 years of age has not been established.

**WARNINGS**

**Clinical Worsening and Suicide Risk**

Doxepin HCl is contraindicated in patients with glaucoma or a tendency towards ocular hypotension activity among Asians. African-Maori antidepressants should be used, particularly in older patients. Doxepin HCl is contraindicated in patients who are pregnant or breast-feeding. Doxepin HCl is not recommended for use in pediatric patients, except under the close observation and communication with the prescriber.

**Precautions**

Use in Geriatrics: Doxepin HCl is not recommended for use in elderly patients. (See WARNINGS: Clinical Worsening and Suicide Risk: Information for Patients, and PRECAUTIONS: Pediatric Use).

**DESCRIPTION**

Doxepin hydrochloride is a dibenzoxepin derivative and is the first of the TCAs, primarily metabolized by a CYP2D6-dependent inhibitor. The current hypothesis is that the clinical effects are due, at least in part, to influences on the adrenergic activity at the post-synaptic level, which in susceptible individuals may lead to an increase in extrapyramidal symptoms. The risk of extrapyramidal symptoms may be increased in susceptible individuals who are receiving concurrent treatment with other drugs that block the DA 2 receptor.

**CLINICAL PHARMACOLOGY**

The mechanism of action of doxepin HCl is not definitely established. It is used primarily as an antidepressant. It is a centrally active, tricyclic antidepressant (TCA) and an antihistaminergic agent that inhibits the reuptake of norepinephrine and serotonin. In clinical studies, doxepin HCl has been shown to be effective in the treatment of depression and certain other psychiatric disorders.

**EFFICACY**

The efficacy of doxepin HCl in the treatment of unipolar major depressive disorder (MDD) has been demonstrated in controlled clinical trials, and it has been shown to be effective in the treatment of panic disorder and obsessive-compulsive disorder (OCD). Doxepin HCl is effective in the treatment of major depression in adults, adolescents, and young adults within 12 to 14 days of starting therapy. The efficacy of doxepin HCl in adult outpatients with major depressive disorder has been demonstrated. Treatment of major depressive disorder (MDD) has been shown to have a positive effect on depressive symptoms, quality of life, and work productivity. Doxepin HCl has also been shown to be effective in the treatment of anxiety disorders, including generalized anxiety disorder (GAD) and post-traumatic stress disorder (PTSD).

**SIDE EFFECTS**

The most common side effects of doxepin HCl are somnolence, dry mouth, urinary retention, and constipation. Other possible side effects include dizziness, orthostatic hypotension, dry mouth, urination difficulty, constipation, nausea, vomiting, diarrhea, and allergic reactions. Rare side effects include skin rash, fever, and allergic reactions. Doxepin HCl is generally well-tolerated, with a relatively low incidence of adverse events. However, patients should be monitored for signs of drug-induced liver injury, which may occur with doxepin HCl treatment. Patients with hepatic impairment or those taking concomitant medications that may increase the risk of liver toxicity should be closely monitored.

**PRECAUTIONS**

Information for Patients: Doxepin HCl is not recommended for use in children under 12 years of age. The safety and effectiveness of doxepin HCl in children under 12 years of age have not been established.

**Drug Interactions**

Doxepin HCl interacts with a variety of other drugs, including other TCAs, monoamine oxidase inhibitors (MAOIs), methylphenidate, lithium, and levodopa. Doxepin HCl is primarily metabolized by CYP3A4 and CYP2C19, and its metabolites are primarily excreted in the urine. These interactions may affect the therapeutic and adverse effects of doxepin HCl. Patients should be monitored for signs of drug interactions, and appropriate dose adjustments or discontinuation of concomitant medications should be considered.

**Cimetidine**

Patients with hepatic impairment or those taking concomitant medications that may increase the risk of liver toxicity should be closely monitored. Patients should be monitored for signs of drug interactions, and appropriate dose adjustments or discontinuation of concomitant medications should be considered.

**Tolazamide**

A dose of severe hypoglycemia has been reported in a type II diabetic patient treated with doxepin HCl. The incidence of hypoglycemia may be increased in patients taking doxepin HCl concomitantly with tolazamide. Patients should be monitored for signs of hypoglycemia, and appropriate dose adjustments or discontinuation of concomitant medications should be considered.

**Bromocriptine**

Bromocriptine is a dopamine agonist used to treat Parkinson's disease and hyperprolactinemia. The incidence of hypoglycemia may be increased in patients taking doxepin HCl concomitantly with bromocriptine. Patients should be monitored for signs of hypoglycemia, and appropriate dose adjustments or discontinuation of concomitant medications should be considered.

**Botulism**

Doxepin HCl is not recommended for use in patients with botulism or other mimics of botulism. Patients should be monitored for signs of drug interactions, and appropriate dose adjustments or discontinuation of concomitant medications should be considered.

**Seizures**

Doxepin HCl is not recommended for use in patients with a history of seizures or a history of alcohol or drug withdrawal syndrome. Patients should be monitored for signs of drug interactions, and appropriate dose adjustments or discontinuation of concomitant medications should be considered.

**Alcohol**

Doxepin HCl is not recommended for use in patients with alcohol dependence or alcoholism. Patients should be monitored for signs of drug interactions, and appropriate dose adjustments or discontinuation of concomitant medications should be considered.

**Pregnancy**

Doxepin HCl is not recommended for use in pregnancy. Patients should be monitored for signs of drug interactions, and appropriate dose adjustments or discontinuation of concomitant medications should be considered.
**OVERDOSAGE**

Deaths may occur from overdose with this class of drugs. Multiple drug ingestions, including doxepin, are associated with a high fatality rate. As the management is complex and often requires a sustained effort, the patient should be placed in a position convenient to the nursing staff for possible resuscitation. Prior to hospitalization, monitoring is required as soon as possible.

**Manifestations:**

Critical manifestations of overdose include: cardiac dysrhythmias, severe hypotension, convulsions, and CNS depression, including coma. Changes in the electrocardiogram, particularly in the T-waves, are strongly indicative of tricyclic antidepressant poisoning.

Other signs of overdose may include: confusion, disturbed consciousness, ataxia, hyperreflexia, diarrhea, vomiting, hyperpyrexia, hyperthermia, hypoglycemia, or any of the symptoms under ADVERSE REACTIONS.

**General Recommendations:**

- Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient’s airway, establish an intravenous line and institute gastric decontamination. A minimum of six hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or hypoglycemia may occur at any time during this period. Extended monitoring is recommended. There are case reports of patients succumbing to fatal cardiac dysrhythmias late after overdose; these patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination. Monitoring of plasma drug levels should not guide management of the patient.

**Gastrointestinal Decontamination**

At patients suspected of tricyclic antidepressant overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If charcoal is used, it should be given prior to lavage. Emesis is contraindicated.

**Cardiovascular**

A maximal limit QRS duration of 10.10 seconds may be the best indication of the severity of the overdose. Intravenous sodium bicarbonate should be used to maintain the serum pH in the range of 7.45 to 7.55. Artificiial ventilation may also be used. Concomitant use of hyperventilation and sodium bicarbonate should be avoided with frequent pH monitoring. A pH > 7.0 or a pCO2 < 20 mm Hg is undesirable. A pH of 7.45 to 7.55 with bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

In rare instances, hemoperitoneum may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis generally have been reported as ineffective in tricyclic antidepressant poisoning.

**CNS**

In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with lorazepam, or if these are ineffective, other anticonvulsants (e.g., phenytoin and phenobarbital). Physostigmine and naloxone should not be used. These patients have been unresponsive to other therapies and only in consultation with a poison control center.

**Psychiatric Follow-Up**

Since overdose is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

**Pediatric Management**

The principles of management of child and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

**DOSAGE AND ADMINISTRATION**

For most patients with illnesses of mild to moderate severity, a starting daily dose of 75 mg or more is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual responses. The usual optimum dose range is 75 mg/day to 150 mg/day in two or more divided doses. It is not unusual for patients to reach a maintenance dose of 150 mg/day. However, the maximum recommended dose is 300 mg/day. This may be reached by using the capsule strengths intended for treatment of agitation only. It is not recommended for maintenance therapy.

**Antianxiety effect is apparent before the antidepressant effect.**

**HOW SUPPLIED**

Doxepin HCI capsules USP, equivalent to 150 mg of doxepin are hard gelatin capsules with white opaque body and blue opaque cap. They are supplied in bottles of 100 (NDC # 4898-222-01), 200 (NDC # 4898-222-01), and 500 (NDC # 4898-222-01).

**Medication Guide**

Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with your or your family member’s antidepressant medicine. The Medication Guide is only about the risks of suicidal thoughts and actions with antidepressant medicines. Talk to your, or your family member’s healthcare provider about:

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illnesses
- What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.

2. Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have or have a family history of bipolar disorder (also called manic-depressive illness) or suicide attempts.

- Pay close attention to any changes, especially sudden changes, in mood, behavior, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
- Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings. Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits if needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worsen, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood
- Visual problems: eye pain, changes in vision, swelling or redness in an eye

What else do I need to know about antidepressant medicines?

- Never stop an antidepressant medicine without first talking to your healthcare provider. Stopping an antidepressant medicine suddenly can cause other problems.
- Visual problems: Only some people are at risk for these problems. You may need to undergo an eye examination to see if you are at risk and receive preventative treatment if you are.
- Antidepressants are medicines used to treat depression and other illnesses. It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.