

average dosages and may obtain satisfactory improvement with 25–50 mg of doxepin daily. The manufacturers state that appropriate dosage in geriatric patients should be selected with caution, usually initiating therapy at the low end of the dosage range since decreased hepatic, renal, or cardiac function occurs more frequently in these patients.

When doxepin is administered as a single daily dose, the maximum daily dose recommended by the manufacturers is 150 mg. Commercially available 150-mg capsules of doxepin are intended for maintenance therapy only and are not recommended for initial therapy. Maximum antidepressant effects may not occur for 2 or more weeks after therapy is begun, although anxiolytic effects may develop more rapidly.

After symptoms are controlled, dosage should be gradually reduced to the lowest level which will maintain relief of symptoms. To avoid the possibility of precipitating withdrawal symptoms, doxepin should not be terminated abruptly in patients who have received high dosages for prolonged periods.

Patients should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Cautions: Precautions and Contraindications, in the Tricyclic Antidepressants General Statement 28:16.04.28.)

Cautions

Doxepin shares the pharmacologic actions and toxic potentials of the tricyclic antidepressants, and the usual precautions of tricyclic antidepressant administration should be observed. Patients should be fully advised about the risks, especially suicidal thinking and behavior (suicidality), associated with tricyclic antidepressant therapy. For a complete discussion, see Cautions: Precautions and Contraindications and Cautions: Pediatric Precautions, in the Tricyclic Antidepressants General Statement 28:16.04.28.

■ **Pediatric Precautions** Safety of doxepin in children younger than 12 years of age has not been established.

The US Food and Drug Administration (FDA) has determined that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. However, FDA also states that depression and certain other psychiatric disorders are themselves associated with an increased risk of suicide. Anyone considering the use of doxepin in a child or adolescent for any clinical use must therefore balance the potential risk of therapy with the clinical need. (See Cautions: Precautions and Contraindications and Cautions: Pediatric Precautions, in the Tricyclic Antidepressants General Statement 28:16.04.28.)

■ **Lactation** Limited data indicate that doxepin and its active *N*-demethylated metabolite are distributed into milk. Sedation and serious respiratory depression were reported in a nursing infant whose mother was receiving 75 mg of doxepin daily; substantial concentrations of the active metabolite of the drug were detected in the infant's serum and urine. In addition, poor sucking and swallowing while nursing, drowsiness, muscle hypotonia, and vomiting were reported in a nursing infant whose mother was receiving 35 mg of doxepin daily. Because of the potential for serious adverse reactions to doxepin and/or its active metabolite in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the woman.

Pharmacokinetics

■ **Absorption** The pharmacokinetics of doxepin have not been extensively studied, but the drug is well absorbed from the GI tract in animals. Peak plasma concentrations usually occur within 2 hours after oral administration of the drug.

■ **Distribution** Doxepin is highly bound to plasma proteins. Limited data indicate that doxepin and its active *N*-demethylated metabolite are distributed into milk in concentrations reportedly ranging from about 30–140% and 10–115%, respectively, of those in maternal serum and that substantial concentrations of the active metabolite have been detected in the serum and urine of nursing infants whose mothers were receiving 75–150 mg of doxepin daily.

■ **Elimination** The plasma half-life of doxepin is 6–24.5 hours. The drug appears to be metabolized via the same pathways as are other tricyclic antidepressants; its *N*-demethylated metabolite is pharmacologically active.

Chemistry and Stability

■ **Chemistry** Doxepin hydrochloride is a dibenzoxepin-derivative tricyclic antidepressant. The drug occurs as a white powder, is freely soluble in water and in alcohol, and has a pK_a of 8. Doxepin hydrochloride oral concentrate has a pH of 4–7.

■ **Stability** Doxepin hydrochloride capsules should be stored in tight, light-resistant containers at a temperature between 15–30°C and the oral concentrate should be stored at a temperature between 20–25°C. Commercially available doxepin hydrochloride capsules have an expiration date of 36 months and the oral concentrate has an expiration date of 24 months following the date of manufacture.

Doxepin hydrochloride oral concentrate is physically incompatible with many carbonated beverages, but is compatible with some other beverages. (See Dosage and Administration: Administration.) Bulk preparation and storage of

dilutions of the commercially available oral concentrate are not recommended by the manufacturers.

For further information on chemistry, pharmacology, pharmacokinetics, uses, cautions, acute toxicity, drug interactions, and dosage and administration of doxepin, see the Tricyclic Antidepressants General Statement 28:16.04.28.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Doxepin Hydrochloride

Oral		
Capsules	10 mg (of doxepin)*	Doxepin Hydrochloride Capsules Sinequan®, Pfizer
	25 mg (of doxepin)*	Doxepin Hydrochloride Capsules Sinequan®, Pfizer
	50 mg (of doxepin)*	Doxepin Hydrochloride Capsules Sinequan®, Pfizer
	75 mg (of doxepin)*	Doxepin Hydrochloride Capsules Sinequan®, Pfizer
	100 mg (of doxepin)*	Doxepin Hydrochloride Capsules Sinequan®, Pfizer
Solution, concentrate	150 mg (of doxepin)*	Doxepin Hydrochloride Capsules Sinequan®, Pfizer
	10 mg (of doxepin) per mL*	Doxepin Hydrochloride Oral Solution (Concentrate) Sinequan® Oral Concentrate, Pfizer

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

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**Imipramine Hydrochloride
Imipramine Pamoate**

■ Imipramine is a dibenzazepine-derivative tricyclic antidepressant.

Dosage and Administration

■ **Administration** Imipramine hydrochloride and imipramine pamoate are administered orally. Although imipramine hydrochloride has been administered in up to 4 divided doses throughout the day, it is long-acting and the entire oral daily dose may be administered at one time. Imipramine pamoate may also be used to administer the daily oral dose of imipramine, but it has no advantages over the hydrochloride. Administration of the entire daily dose at bedtime may reduce daytime sedation; patients who experience insomnia and stimulation may be given the entire daily dose in the morning.

■ **Dosage** Dosage of imipramine salts is expressed in terms of imipramine hydrochloride.

Patients should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Cautions: Precautions and Contraindications, in the Tricyclic Antidepressants General Statement 28:16.04.28.)

Major Depressive Disorder There is a wide range of oral dosage requirements, and dosage must be carefully individualized. Initial dosages of imipramine should be low and generally range from 75–100 mg daily, depending on the severity of the condition being treated. Dosage may be gradually adjusted to the level that produces maximal therapeutic effect with minimal toxicity and may range up to 300 mg daily. Hospitalized patients under close supervision may generally be given higher dosages than outpatients, and manufacturers state that dosages of greater than 200 mg daily are not recommended for outpatients. Geriatric patients should usually be given lower than average dosages. Manufacturers state that therapy should be initiated with 25–50 mg daily as imipramine hydrochloride (e.g., Tofranil®) in these patients and that optimal dosage rarely exceeds 100 mg daily. If the daily dosage is established at 75 mg or more, imipramine pamoate (e.g., Tofranil® PM) may be administered. Maximum antidepressant effects may not occur for 2 or more weeks after therapy is begun.

After symptoms are controlled, dosage should be gradually reduced to the lowest level that will maintain relief of symptoms. If maintenance therapy is