

69-2135-00-1

SINEQUAN®
(doxepin HCl)
CAPSULES
ORAL CONCENTRATE

DESCRIPTION

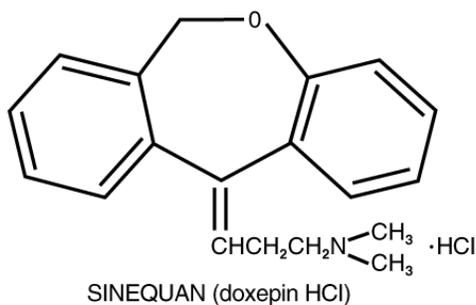
SINEQUAN® (doxepin hydrochloride) is one of a class of psychotherapeutic agents known as dibenzoxepin tricyclic compounds. The molecular formula of the compound is $C_{19}H_{21}NO \cdot HCl$ having a molecular weight of 316. It is a white crystalline solid readily soluble in water, lower alcohols and chloroform.

Inert ingredients for the capsule formulations are: hard gelatin capsules (which may contain Blue 1, Red 3, Red 40, Yellow 10, and other inert ingredients); magnesium stearate; sodium lauryl sulfate; starch.

Inert ingredients for the oral concentrate formulation are: glycerin; methylparaben; peppermint oil; propylparaben; water.

CHEMISTRY

SINEQUAN (doxepin HCl) is a dibenzoxepin derivative and is the first of a family of tricyclic psychotherapeutic agents. Specifically, it is an isomeric mixture of:
1-Propanamine, 3-dibenz[*b,e*]oxepin-11(6*H*)ylidene-*N,N*-dimethyl-, hydrochloride.



ACTIONS

The mechanism of action of SINEQUAN (doxepin HCl) is not definitely known. It is not a central nervous system stimulant nor a monoamine oxidase inhibitor. The current hypothesis is that the clinical effects are due, at least in part, to influences on the adrenergic activity at the synapses so that deactivation of norepinephrine by reuptake into the nerve terminals is prevented. Animal studies suggest that doxepin HCl does not appreciably antagonize the antihypertensive action of guanethidine. In animal studies anticholinergic, antiserotonin and antihistamine effects on smooth muscle have been demonstrated. At higher than usual clinical doses, norepinephrine response was potentiated in animals. This effect was not demonstrated in humans.

At clinical dosages up to 150 mg per day, SINEQUAN can be given to man concomitantly with guanethidine and related compounds without blocking the antihypertensive effect. At dosages above 150 mg per day blocking of the antihypertensive effect of these compounds has been reported.

SINEQUAN is virtually devoid of euphoria as a side effect. Characteristic of this type of compound, SINEQUAN has not been demonstrated to produce the physical tolerance or psychological dependence associated with addictive compounds.

INDICATIONS

SINEQUAN is recommended for the treatment of:

1. Psychoneurotic patients with depression and/or anxiety.
2. Depression and/or anxiety associated with alcoholism (not to be taken concomitantly with alcohol).
3. Depression and/or anxiety associated with organic disease (the possibility of drug interaction should be considered if the patient is receiving other drugs concomitantly).
4. Psychotic depressive disorders with associated anxiety including involuntional depression and manic-depressive disorders.

The target symptoms of psychoneurosis that respond particularly well to SINEQUAN include anxiety, tension, depression, somatic symptoms and concerns, sleep disturbances, guilt, lack of energy, fear, apprehension and worry.

Clinical experience has shown that SINEQUAN is safe and well tolerated even in the elderly patient. Owing to lack of clinical experience in the pediatric population, SINEQUAN is not recommended for use in children under 12 years of age.

CONTRAINDICATIONS

SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

WARNINGS

The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition (see PRECAUTIONS—Geriatric Use).

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There has been a report of apnea and drowsiness occurring in a nursing infant whose mother was taking SINEQUAN.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

PRECAUTIONS

Drug Interactions: *Drugs Metabolized by P450 2D6:* The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7-10% of Caucasians are so-called “poor metabolizers”); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with any of the SSRIs and also in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from

fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be co-administered with another drug known to be an inhibitor of P450 2D6.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Cimetidine: Cimetidine has been reported to produce clinically significant fluctuations in steady-state serum concentrations of various tricyclic antidepressants. Serious anticholinergic symptoms (i.e., severe dry mouth, urinary retention and blurred vision) have been associated with elevations in the serum levels of tricyclic antidepressant when cimetidine therapy is initiated. Additionally, higher than expected tricyclic antidepressant levels have been observed when they are begun in patients already taking cimetidine. In patients who have been reported to be well controlled on tricyclic antidepressants receiving concurrent cimetidine therapy, discontinuation of cimetidine has been reported to decrease established steady-state serum tricyclic antidepressant levels and compromise their therapeutic effects.

Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdose. This is especially important in patients who may use alcohol excessively.

Tolazamide: A case of severe hypoglycemia has been reported in a type II diabetic patient maintained on tolazamide (1 gm/day) 11 days after the addition of doxepin (75 mg/day).

Drowsiness: Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Sedating drugs may cause confusion and oversedation in the elderly; elderly patients generally should be started on low doses of SINEQUAN and observed closely. (See PRECAUTIONS—Geriatric Use.)

Suicide: Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Psychosis: Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Geriatric Use: A determination has not been made whether controlled clinical studies of SINEQUAN included sufficient numbers of subjects aged 65 and over to define a difference in response from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

The extent of renal excretion of SINEQUAN has not been determined. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selections.

Sedating drugs may cause confusion and oversedation in the elderly; elderly patients generally should be started on low doses of SINEQUAN and observed closely. (See WARNINGS.)

ADVERSE REACTIONS

NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN (doxepin HCl).

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, extrapyramidal symptoms, seizures, tardive dyskinesia, and tremor.

Cardiovascular: Cardiovascular effects including hypotension, hypertension, and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See Anticholinergic Effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone secretion have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, headache, exacerbation of asthma, and hyperpyrexia (in association with chlorpromazine) have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

DOSAGE AND ADMINISTRATION

For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed, the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

OVERDOSAGE

Deaths may occur from overdose with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic antidepressant overdose. As the management is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after tricyclic antidepressant overdose; therefore, hospital 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 QRS axis or width, are clinically significant indicators of tricyclic antidepressant toxicity.

Other signs of overdose may include: confusion, disturbed concentration, transient visual hallucinations, dilated pupils, agitation, hyperactive reflexes, stupor, drowsiness, muscle rigidity, vomiting, hypothermia, hyperpyrexia, or any of the symptoms listed under ADVERSE REACTIONS.

General Recommendations:

General: Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line and initiate 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 conduction blocks, and seizures is strongly advised. If signs of toxicity occur at any time during this period, extended monitoring is recommended. There are case reports of patients succumbing to fatal 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: All patients suspected of tricyclic antidepressant overdose should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. Emesis is contraindicated.

Cardiovascular: A maximal limb-lead QRS duration of ≥ 0.10 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. If the pH response is inadequate, hyperventilation may also be used. Concomitant use of hyperventilation and sodium bicarbonate should be done with extreme caution, with frequent pH monitoring. A pH > 7.60 or a $pCO_2 < 20$ mm Hg is undesirable. Dysrhythmias unresponsive to sodium 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, hemoperfusion 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 benzodiazepines, or if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in consultation with a poison control center.

Psychiatric Follow-up: Since overdosage 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 overdoses are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

HOW SUPPLIED

SINEQUAN® is available as capsules containing doxepin HCl equivalent to:

10 mg– 100’s (NDC 0049-5340-66)	25 mg–	100’s (NDC 0049-5350-66)
50 mg– 100’s (NDC 0049-5360-66)		
5000’s (NDC 0049-5360-94)		
75 mg– 100’s (NDC 0049-5390-66)		
100 mg– 100’s (NDC 0049-5380-66)		
150 mg– 50’s (NDC 0049-5370-50)		

SINEQUAN® Oral Concentrate is available in 120 mL bottles (NDC 0049-5100-47) with an accompanying dropper calibrated at 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg. Each mL contains doxepin HCl equivalent to 10 mg doxepin. Just prior to administration, SINEQUAN® Oral Concentrate should be diluted with approximately 120 mL of water, whole or skimmed milk, or orange, grapefruit, tomato, prune or pineapple juice. SINEQUAN® Oral Concentrate is not physically compatible with a number of carbonated beverages. For those patients requiring antidepressant therapy who are on methadone maintenance, SINEQUAN® Oral Concentrate and methadone syrup can be mixed together with Gatorade®, lemonade, orange juice, sugar water, Tang®, or water; but not with grape juice. Preparation and storage of bulk dilutions is not recommended.

Rx only

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