PFIZER
SINEQUAN®
Doxepin

1. NAME OF THE MEDICINAL PRODUCT

SINEQUAN®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient: doxepin hydrochloride (HCl)

Capsules containing doxepin HCl equivalent to 10 mg and 25 mg doxepin.

3. PHARMACEUTICAL FORM

Capsules.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Doxepin is a safe and effective psychotherapeutic agent for the treatment of patients with a wide range of psychoneurotic disorders where anxiety and/or depression are prominent symptoms.

Thus, where these prime symptoms are present, the compound has been shown to be of value in patients with anxiety neuroses, with and without somatic symptoms; reactive depression; mixed anxiety depression; and patients with alcoholism with anxiety and/or depression.

In addition, doxepin is similarly effective in the treatment of patient suffering from psychotic depression, including endogenous depression, involutional melancholia, senile depression, postpartum depression, and for the treatment of manic-depressive reactions during the depressed phase.

Target symptoms that respond to treatment include: anxiety, depression, tension, apprehension, agitation, functional somatic complaints, insomnia, loss of interest, guilt, psychomotor retardation, and hypochondriasis.

Doxepin may be used with benefit where symptoms are of short or long duration prior to treatment and in patients with a wide range of intensity of illness.

As with other psychotherapeutic agents, the degree of response varies with each patient. In patients exhibiting a beneficial response, this may be seen within a few days of commencing therapy, while others may not respond for two weeks or longer.

4.2 Posology and Method of Administration

Oral use

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 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 to 50 mg/day.

The total daily dosage of doxepin 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.

Use in the elderly

Dosage reduction may be required in elderly patients.

Use in children and adolescents under 18 years of age

Doxepin should not be used in the treatment of children and adolescents under the age of 18 years. (See section **4.4 Special warnings and precautions for use – *Use in children and adolescents under 18 years of age***)

Use in patients with impaired hepatic function

Dosage reduction may be required in patients with hepatic impairment.

Use in patients with insomnia or experiencing drowsiness

In patients where insomnia is a troublesome symptom, it is recommended that the total daily dose be divided so that a higher proportion is given for the evening dose; alternatively, if drowsiness is experienced as a side effect of treatment, doxepin may be administered by this regimen, or the dosage may be reduced.

4.3 Contraindications

Doxepin is contraindicated in individuals who have shown hypersensitivity to TCAs (tricyclic antidepressants), doxepin, or any of the inactive ingredients.

Doxepin is also contraindicated in patients with glaucoma or a tendency for urinary retention. These disorders should be ruled out, particularly in elderly patients.

4.4 Special warnings and special precautions for use

General:

The once-a-day dosage regimen of doxepin 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. It may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen should increased symptoms of psychosis or shift to manic symptomatology occur.

The use of doxepin on a once-a-day dosage regimen in elderly patients should be adjusted carefully based on the patient's condition.

Patients should be warned that drowsiness may occur with the use of this drug (see Section **4.2 Posology and Method of Administration**).

Alcohol ingestion may increase the danger inherent in any intentional or unintentional doxepin overdosage. This is especially important in patients who may use alcohol excessively.

Caution should be exercised in the use of doxepin in patients with severe cardiovascular disease, hepatic and/or renal impairment.

Use in children and adolescents under 18 years of age:

Doxepin should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behavior (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behavior and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation, and cognitive and behavioral development are lacking.

Use in young adults (18-25 years of age):

An additional analysis of pooled data of currently available antidepressants showed an increased risk of suicidal thinking and behavior when compared to placebo in young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Currently, data are insufficient to quantify an increased risk of suicidal thinking and behavior associated with doxepin treatment. Nevertheless, anyone considering the use of doxepin in young adults must balance this potential risk with the clinical need.

Suicide/suicidal thoughts or clinical worsening:

Depression is associated with an increased risk of suicidal thoughts, self harm, and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patient (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behavior or thoughts and unusual changes in behavior and to seek medical advice immediately if these symptoms present.

4.5 Interaction with other medicaments and other forms of interaction

Drugs Metabolized by cytochrome P450 (CYP) 2D6:

Doxepin, like other tricyclic antidepressants (TCAs), is metabolized by CYP2D6. Inhibitors or substrates of CYP2D6 (i.e., quinidine, selective serotonin reuptake inhibitors [SSRIs]) may increase the plasma concentration of TCAs when administered concomitantly. The extent of interaction depends on the variability of effect on CYP2D6 and the therapeutic index of the TCA. The clinical significance of this interaction with doxepin has not been systematically evaluated.

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 doxepin. 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.

Alcohol:

Patients should be cautioned that their response to alcohol may be potentiated.

Guanethidine:

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

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 antidepressants when cimetidine therapy is initiated. Additionally, higher than expected tricyclic antidepressant levels have been seen in patients receiving concurrent cimetidine therapy. Discontinuation of cimetidine has been reported to decrease established steady-state serum tricyclic antidepressant levels and compromise their therapeutic effects.

Tolazamide:

A case of severe hypoglycemia, 11 days after the addition of doxepin (75 mg/day), has been reported in a non-insulin dependent diabetic patient maintained on tolazamide (1 gm/day).

4.6 Pregnancy and Lactation

Usage in pregnancy

Doxepin crosses the placenta. The safety of doxepin during pregnancy has not been established in clinical trials and therefore, it should not be used in women of childbearing

potential, unless, in the opinion of the physician, the potential benefits to the patient outweigh the possible risks to the fetus.

Usage in nursing mothers

Limited data indicate that doxepin and its active metabolite desmethyldoxepin are excreted in breast milk. There has been a report of apnea and drowsiness occurring in a nursing infant whose mother was taking doxepin. Because of potential for adverse effects to the nursing infant, breast-feeding is not recommended during doxepin therapy.

4.7 Effects on ability to drive and use machines

Patients should be warned that drowsiness may occur with the use of this drug and cautioned against driving a car or operating dangerous machinery while taking this drug.

4.8 Undesirable effects

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

Anticholinergic effects including 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.

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

Metabolism and nutrition disorders: Anorexia has been reported.

Psychiatric disorders: Agitation, confusion, disorientation, hallucinations.

Nervous system disorders: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are ataxia, extrapyramidal symptoms, numbness, paresthesia, seizures, tardive dyskinesia, and tremor. Taste disturbances have also been reported.

Cardiac disorders: Cardiovascular effects including tachycardia have been reported occasionally.

Vascular disorders: Hypertension and hypotension have been reported occasionally.

Gastrointestinal disorders: Aphthous stomatitis, diarrhea, indigestion, nausea, and vomiting have been reported.

Skin and subcutaneous disorders: Photosensitization, pruritus, and skin rash have occasionally occurred.

General disorders and administration site conditions: Facial edema has occasionally occurred. Withdrawal symptoms (abrupt cessation of treatment after prolonged administration may produce nausea, headache, and malaise; theses are not indicative of addiction).

The following adverse reactions have been reported with tricycilc administration: enlargement of breasts and galactorrhea in the female, gynecomastia in males, raising or lowering of blood sugar levels, raised or lowered libido, testicular swelling, and the syndrome of inappropriate antidiuretic hormone secretion.

The following adverse reactions have been occasionally observed in association with chlorpromazine: alopecia, chills, dizziness, exacerbation of asthma, fatigue, flushing, headache, hyperpyrexia, jaundice, sweating, tinnitus, weakness, and weight gain.

4.9 Overdose

Signs and symptoms

1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.

2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

Deaths have been reported involving overdoses of doxepin.

Management and treatment

1. Mild: Observation including EKG monitoring and supportive therapy is all that is usually necessary.

2. Severe: Medical management of severe doxepin overdosage consists of aggressive supportive therapy. Gastric lavage should be performed with appropriate precautions to prevent pulmonary aspiration, even though doxepin in therapeutic dosages is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent(s). Convulsions may respond to standard anticonvulsant therapy; however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of doxepin.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Doxepin hydrochloride is one of a class of psychotherapeutic agents known as dibenzoxepin tricyclic compounds.

The mechanism of action of doxepin 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 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.

5.2 Pharmacokinetic properties

Absorption:

Doxepin is well absorbed from the gastrointestinal tract. Approximately 55-87% of orally administered doxepin undergoes first pass metabolism in the liver, forming the primary active metabolite desmethyldoxepin.

Distribution:

In healthy volunteers, a single oral dose of 75 mg resulted in peak plasma concentrations for doxepin ranging from 8.8-45.8 ng/ml (mean 26.1 ng/ml). Peak levels were reached between 2 and 4 hours (mean 2.9 hours) after administration. Peak levels for the primary metabolite desmethyldoxepin ranged from 4.8-14.5 ng/ml (mean 9.7 ng/ml) and were achieved between 2 and 10 hours after administration. The mean apparent volume of distribution for doxepin is approximately 20 l/kg. The protein binding for doxepin is approximately 76%.

Metabolism and Excretion:

Paths of metabolism of doxepin include demethylation, N-oxidation, hydroxylation and glucuronide formation. In healthy volunteers, the plasma elimination half-life of doxepin ranged from 8 to 24 hours (mean 17 hours). The half-life of desmethyldoxepin ranged from 33-80 hours (mean 51 hours). Mean plasma clearance for doxepin is approximately 0.84 l/kg hr. Doxepin is excreted primarily in the urine, mainly as its metabolites, either free or in conjugate form.

5.3. Preclinical safety data

Reproduction studies have been performed in rats, rabbits, and monkeys and there was no evidence of harm to the animal fetus. The relevance to humans is not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

10mg Capsules: Corn (maize) starch, lactose, magnesium stearate and sodium lauryl sulphate

25mg Capsules: Corn (maize) starch, lactose, colloidal silicon dioxide, magnesium stearate and sodium lauryl sulphate

6.2 Incompatibilities

None.

6.3 Shelf-life

Refer to outer carton for shelf-life.

6.4 Special storage precautions

Refer to outer carton for storage condition.

6.5 Nature and contents of container

Doxepin 10mg and 25mg capsules are packed in PVC/Aluminum foil blisters.
Package sizes: 100's and 500's / carton

6.6 Instructions for use/handling

To be dispensed only by or on the prescription of a physician.
Keep out of the reach of children.

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