PRODUCT MONOGRAPH

ZONALON CREAM 5%

GENERIC NAME

DOXEPIN HYDROCHLORIDE CREAM 5%

THERAPEUTIC CLASSIFICATION

TOPICAL ANTIPRURITIC

Valeant Canada LP.
Montreal, Quebec
H4R 2P9

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PRODUCT MONOGRAPH

PROPER NAME: ZONALON CREAM (DOXEPIN HCL CREAM 5%)

THERAPEUTIC CLASSIFICATION: TOPICAL ANTIPRURITIC

ACTION

Doxepin, a dibenzoxepin-derivative tricyclic compound, is a topical antipruritic. While the exact mechanism of antipruritic activity is unknown, Doxepin exhibits potent histamine H1 and H2 receptor antagonist activity. Although the sedative effect of systemically absorbed Doxepin may contribute to the drug's antipruritic activity, the antipruritic efficacy of Doxepin reportedly does not appear to depend on a sedative effect.

INDICATIONS

ZONALON Cream 5% (Doxepin HCL Cream) is indicated for the short term (up to 8 days) topical relief of histamine mediated pruritus of moderate severity accompanying conditions such as eczematous dermatitis.

CONTRAINDICATIONS

ZONALON Cream is contraindicated in individuals who have shown hypersensitivity to the drug or to other dibenzoxepin compounds.

ZONALON Cream is not recommended in children under the age of 12 because safety and efficacy in this age group have not been established.

Because Doxepin HC1 has an anticholinergic affect and because significant plasma levels of Doxepin are detectable after topical ZONALON CREAM application, the use of ZONALON CREAM is contraindicated in patients with glaucoma or a tendency to urinary retention.

ZONALON CREAM is contraindicated in individuals who have shown previous sensitivity to any of its components.

WARNINGS

PREGNANCY AND LACTATION: The safety of ZONALON Cream during pregnancy and lactation has not been established and therefore, it should not be used in women of child bearing potential or nursing mothers unless in the opinion of the physician, the potential benefit to the patient outweighs the possible hazards to the fetus.

Drowsiness occurs in over 20% of patients treated with ZONALON Cream 5%, especially in patients receiving treatment to greater than 10% of their body surface area. Patients should be warned of this possibility and cautioned against driving a motor vehicle or operating hazardous machinery while being treated with ZONALON Cream.

If excessive drowsiness occurs it may be necessary to reduce the number of applications, the amount of cream applied, and/or the percentage of body surface area treated.

MAO INHIBITORS: Serious side effects and even death have been reported following the concomitant use of certain orally administered drugs chemically related to Doxepin and MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the initiation of treatment with ZONALON Cream 5%.

CIMETIDINE: Cimetidine has been reported to produce clinically significant fluctuations in steady-state serum concentrations of various tricyclic antidepressants when taken orally. Serious anticholinergic symptoms have been associated with elevations in serum levels of orally administered tricyclic antidepressants when cimetidine therapy is initiated. Higher than expected tricyclic antidepressant levels have been observed 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.

The relevance of concurrent administration of cimetidine on the antipruritic effectiveness of Zonalon Cream, applied topically, is not known.

ALCOHOL: Alcohol ingestion has exacerbated the potential sedative effects of ZONALON Cream 5%, particularly in those individuals who use alcohol excessively.

CNS DRUGS: CNS drugs Patient should be warned that the effects of other drugs acting on the central nervous system such as barbiturates and other CNS depressants, are potentiated by ZONALON Cream.

PRECAUTIONS

Studies have not been done examining drug interactions with Doxepin HCL Cream. In an eight day 40 patient percutaneous absorption study, none of the patients who applied Doxepin Cream 5% four times each day had blood levels which reached the antidepressant therapeutic range for oral Doxepin.

Patients should also be warned that the effects of alcoholic beverages can be potentiated when using ZONALON Cream, 5%.

Local adverse effects have been reported infrequently with the use of topical ZONALON Cream 5%, but may occur more frequently with the use of occlusive dressings. Occlusive dressings may increase the absorption of most topical drugs; therefore, occlusive dressing should not be used with ZONALON CREAM.

ADVERSE EFFECTS

Local reactions are listed in a decreasing order of occurrence and include: burning, stinging, irritation, tingling and local rash.

Systemic effects which have been observed with the topical use of ZONALON Cream 5%, include anticholinergic effects: dry mouth, thirst, taste changes, dry eyes. Central nervous system (CNS) effects including drowsiness, asthenia, headaches, fever, dizziness and gastrointestinal effects were nausea, dyspepsia, vomiting and diarrhea.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

SYMPTOMS: Symptoms of overdosage with ZONALON Cream include an increase in any of the reported adverse reactions, primarily excessive sedation and anticholinergic effects such as blurred vision and dry mouth. Other effects may include: pronounced tachycardia, hypotension and/or extrapyramidal symptoms.

DOSAGE AND ADMINISTRATION

ZONALON Cream 5% should be applied to the affected area in a thin film three to four times daily with at least 3 or 4 hours interval between applications. ZONALON cream should be used for a short term no longer than eight days. Chronic use beyond eight days may result in higher systemic levels.

Clinical experience has shown that drowsiness is significantly more common in patients applying treatments to over 10% of body surface area, (BSA) therefore patients with over 10% of BSA affected should be especially cautioned concerning possible drowsiness.

If excessive drowsiness occurs it may be necessary to reduce BSA treated, reduce the number of applications per day, and/or reduce the amount of cream applied.

Occlusal dressing may also increase the absorption of most topical drugs therefore occlusive dressing should not be used with ZONALON CREAM.

AVAILABILITY

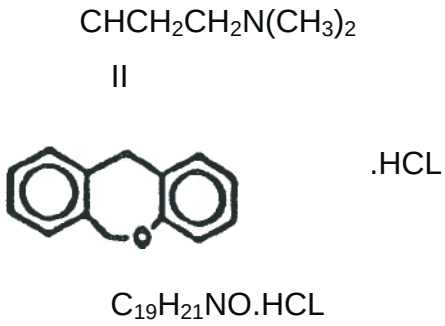
ZONALON Cream, Doxepin HCL Cream 5%, is available in 30g aluminum tubes.

DRUG SUBSTANCE

PROPER NAME: Doxepin Hydrochloride

CHEMICAL NAME: 1-Propanamine, 3-dibenz (b, e) oxepin 11-(6H) ylidene-N,N-dimethyl, hydrochloride

STRUCTURAL FORMULA



$C_{19}H_{21}NO.HCL$

MOLECULAR WEIGHT: 315.8

PHYSICAL AND CHEMICAL CHARACTERISTICS: Doxepin HCL is a white crystalline powder with a slight amine like odour. Doxepin HCL is soluble in 1.5 of water, 1 in 1 of alcohol, 1 in 2 of chloroform. The melting point of Doxepin HCL is 185 to 191.

PHARMACOLOGY

PRIMARY TOPICAL ACTIVITY: Doxepin has potent histamine H1 and H2 blocking actions and these effects would result in pharmacological effects commonly associated with antihistamines. Doxepin HCL has been shown to have a high affinity for histamine H1 receptors (about 800 times greater than diphenhydramine and 50 times greater than hydroxyzine).

SECONDARY SYSTEMIC ACTIVITY: Doxepin is a tricyclic antidepressant which is available for oral treatment of depression and/or anxiety. Doxepin HCL has also been shown to have sedative properties.

The antidepressant clinical effects are due to influences on the adrenergic activity at the synapse so that the deactivation of norepinephrine by reuptake into the nerve terminals is prevented.

As with other antidepressant compounds, Doxepin is also a potent anti-muscarinic receptor blocker which may cause blurred vision, dry mouth, constipation and urinary retention.

Doxepin also acts on the cardiovascular system and hypotension and tachycardia have been reported. These cardiovascular effects may be associated with both inhibition or norepinephrine reuptake and blockage or muscarinic receptors.

In 12 pruritic eczema patients treated with ZONALON CREAM PLASMA Doxepin concentrations ranged from non-detectable to 47ng/mL from percutaneous absorption. Target therapeutic plasma levels of ORAL Doxepin HC1 for the treatment of depression range from 30-150 ng/mL.

TOXICOLOGY

ACUTE TOXICITY STUDIES: Doxepin HCL has a relative high margin of safety. The oral LD50 was 148 to 178 mg /kg in mice, 346 to 460 mg/kg in rats and approximately 200 mg/kg in dogs.

SUBACUTE TOXICITY STUDIES: No macroscopic, microscopic, hematologic or biochemical changes were observed in dogs given 25 to 50 mg/kg daily for 30 days. Mild sedation and vomiting occurred at a dose of 25 mg/kg and increased heart rate miosis, sedation and twitching was observed at a dose of 50 mg/kg.

CHRONIC TOXICITY: Dogs were given Doxepin HCL at doses of 50 mg/kg, 25 mg/kg, or 5 mg/kg for one year. Dogs given 5 mg/kg were practically asymptomatic. There were occasional episodes of vomiting at 25 mg/kg. At the highest dose of 50 mg/kg, there was ptosis, sedation, tremors and vomiting. Rats fed 100 mg/kg for 18 months demonstrated fatty metamorphosis of the liver in males and inhibition of body weight gain in females.

REPRODUCTION STUDIES: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no impaired fertility or evidence of teratogenic effect to the animal fetus.

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