

Serax® (oxazepam) Capsules and Tablets

SAMPLE



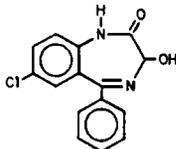
DESCRIPTION

Serax is the first of a chemical series of compounds known as the 3-hydroxybenzodiazepinones. A therapeutic agent providing versatility and flexibility in control of common emotional disturbances, this product exerts prompt action in a wide variety of disorders associated with anxiety, tension, agitation, and irritability, and anxiety associated with depression. In tolerance and toxicity studies on several animal species, this product reveals significantly greater safety factors than related compounds (chlordiazepoxide and diazepam) and manifests a wide separation of effective doses and doses inducing side effects.

Serax capsules contain 10 mg, 15 mg, or 30 mg oxazepam. The inactive ingredients present are FD&C Red 40, gelatin, lactose, titanium dioxide, and other ingredients. Each dosage strength also contains the following:
10 mg—D&C Red 22, D&C Red 28, and FD&C Blue 1;
15 mg—FD&C Yellow 6;
30 mg—D&C Red 28 and FD&C Blue 1.

Serax tablets contain 15 mg oxazepam. The inactive ingredients present are FD&C Yellow 5, lactose, magnesium stearate, methylcellulose, and polacrillin potassium.

Serax is 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepin-2-one. A white crystalline powder with a molecular weight of 286.7, its structural formula is as follows:



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APPROVED

Serax®
(oxazepam) 
Capsules and Tablets
Cl 5186-3



CLINICAL PHARMACOLOGY

Pharmacokinetic testing in twelve volunteers demonstrated that when given as a single 30 mg dose, the capsule, tablet, and suspension were equivalent in extent of absorption. For the capsule and tablet, peak plasma levels averaged 450 ng/mL and were observed to occur about 3 hours after dosing. The mean elimination half-life for oxazepam was approximately 8.2 hours (range 5.7 to 10.9 hours).

This product has a single, major inactive metabolite in man, a glucuronide excreted in the urine.

Age (<80 years old) does not appear to have a clinically significant effect

on oxazepam kinetics. A statistically significant increase in elimination half-life in the very elderly (>80 years of age) as compared to younger subjects has been reported, due to a 30% increase in volume of distribution, as well as a 50% reduction in unbound clearance of oxazepam in the very elderly. (see PRECAUTIONS, Geriatric Use).

ANIMAL PHARMACOLOGY AND TOXICOLOGY

In mice, Serax exerts an anticonvulsant (anti-Metrazol®) activity at 50-percent-effective doses of about 0.6 mg/kg orally. (Such anticonvulsant activity of benzodiazepines correlates with their tranquilizing properties.) To produce ataxia (rotarod test) and sedation (abolition of spontaneous motor activity), the 50-percent-effective doses of this product are greater than 5 mg/kg orally. Thus, about ten times the therapeutic (anticonvulsant) dose must be given before ataxia ensues, indicating a wide separation of effective doses and doses inducing side effects.

In evaluation of antianxiety activity of compounds, conflict behavioral tests

in rats differentiate continuous response for food in the presence of anxiety-provoking stress (shock) from drug-induced motor incoordination. This product shows significant separation of doses required to relieve anxiety and doses producing sedation or ataxia. Ataxia-producing doses exceed those of related CNS-acting drugs.

Acute oral LD₅₀ in mice is greater than 5000 mg/kg, compared to 800 mg/kg for a related compound (chlordiazepoxide).

Subacute toxicity studies in dogs for four weeks at 480 mg/kg daily showed no specific changes; at 960 mg/kg two out of eight died with evidence of circulatory collapse. This wide margin of safety is significant compared to chlordiazepoxide HCl, which showed nonspecific changes in six dogs at 80 mg/kg. On chlordiazepoxide, two out of six died with evidence of circulatory collapse at 127 mg/kg, and six out of six died at 200 mg/kg daily. Chronic toxicity studies of Serax in dogs at 120 mg/kg/day for 52 weeks produced no toxic manifestation.

Fatty metamorphosis of the liver has been noted in six-week toxicity studies in rats given this product at 0.5% of the diet. Such accumulations of fat are considered reversible, as there is no liver necrosis or fibrosis.

Breeding studies in rats through two successive litters did not produce fetal abnormality.

Oxazepam has not been adequately evaluated for mutagenic activity.

In a carcinogenicity study, oxazepam was administered with diet to rats for two years. Male rats receiving 30 times the maximum human dose showed a statistical increase, when compared to controls, in benign thyroid follicular cell tumors, testicular interstitial cell adenomas, and prostatic adenomas. An earlier published study reported that mice fed dietary dosages of 35 or 100 times the human daily dose of oxazepam for 9 months developed a dose-related increase in liver adenomas.¹ In an independent analysis of some of the microscopic slides from this mouse study, several of these tumors were classified as liver carcinomas. At this time, there is no evidence that clinical use of oxazepam is associated with tumors.

INDICATIONS

Serax (oxazepam) is indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

Anxiety associated with depression is also responsive to Serax therapy.

This product has been found particularly useful in the management of anxiety, tension, agitation, and irritability in older patients.

Alcoholics with acute tremulousness, inebriation, or with anxiety associated with alcohol withdrawal are responsive to therapy.

The effectiveness of Serax in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

History of previous hypersensitivity reaction to oxazepam. Oxazepam is not indicated in psychoses.

WARNINGS

As with other CNS-acting drugs, patients should be cautioned against driving automobiles or operating dangerous machinery until it is known that they do not become drowsy or dizzy on oxazepam therapy.

Patients should be warned that the effects of alcohol or other CNS-depressant drugs may be additive to those of Serax, possibly requiring adjustment of dosage or elimination of such agents.

Physical and Psychological Dependence

Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, tremor, abdominal and muscle cramps, vomiting, and sweating), have occurred following abrupt discontinuance of oxazepam. The more severe withdrawal symptoms have usually been limited to those patients who received excessive doses over an extended period of time. Generally milder withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage-tapering schedule followed. Addiction-prone individuals (such as drug addicts or alcoholics) should be under careful surveillance when receiving oxazepam or other psychotropic agents because of the predisposition of such patients to habituation and dependence.

USE IN PREGNANCY

An increased risk of congenital malformations associated with the use of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) during the first trimester of pregnancy has been suggested in several studies. Serax, a benzodiazepine derivative, has not been studied adequately to determine whether it, too, may be associated with an increased risk of fetal abnormality. Because use of these





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drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physician about the desirability of discontinuing the drug.

PRECAUTIONS

General

Although hypotension has occurred only rarely, oxazepam should be administered with caution to patients in whom a drop in blood pressure might lead to cardiac complications. This is particularly true in the elderly patient.

Serax® 15 mg tablets, but none of the other available dosage forms of this product, contain FD&C Yellow 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

Information for Patients

To assure the safe and effective use of Serax (oxazepam), patients should be informed that, since benzodiazepines may produce psychological and physical dependence, it is advisable that they consult with their physician before either increasing the dose or abruptly discontinuing this drug.

Pediatric Use

Safety and effectiveness in pediatric patients under 6 years of age have not been established. Absolute dosage for pediatric patients 6 to 12 years of age is not established.

Geriatric Use

Clinical studies of Serax were not adequate to determine whether subjects aged 65 and over respond differently than younger subjects. Age (<80 years old) does not appear to have a clinically significant effect on oxazepam kinetics (see CLINICAL PHARMACOLOGY).

Clinical circumstances, some of which may be more common in the elderly, such as hepatic or renal impairment, should be considered. Greater sensitivity of some older individuals to the effects of Serax (e.g., sedation, hypotension, paradoxical excitation) cannot be ruled out (see PRECAUTIONS, General; see ADVERSE REACTIONS). In general, dose selection for Serax for elderly patients should be cautious, usually starting at the lower end of the dosing range (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

The necessity for discontinuation of therapy due to undesirable effects has been rare. Transient, mild drowsiness is commonly seen in the first few days of therapy. If it persists, the dosage should be reduced. In few instances, dizziness, vertigo, headache, and rarely syncope have occurred either alone or together with drowsiness. Mild paradoxical reactions, i.e., excitement, stimulation of affect, have been reported in psychiatric patients; these reactions may be secondary to relief of anxiety and usually appear in the first two weeks of therapy.

Other side effects occurring during oxazepam therapy include rare instances of nausea, lethargy, edema, slurred speech, tremor, altered libido, and minor diffuse skin rashes—morbilliform, urticarial, and maculopapular. Such side effects have been infrequent and are generally controlled with reduction of dosage. A case of an extensive fixed drug eruption also has been reported.

Although rare, leukopenia and hepatic dysfunction including jaundice have been reported during therapy. Periodic blood counts and liver-function tests are advisable.

Ataxia with oxazepam has been reported in rare instances and does not appear to be specifically related to dose or age.

Although the following side reactions have not as yet been reported with oxazepam, they have occurred with related compounds (chlordiazepoxide and diazepam): paradoxical excitation with severe rage reactions, hallucinations, menstrual irregularities, change in EEG pattern, blood dyscrasias including agranulocytosis, blurred vision, diplopia, incontinence, stupor, disorientation, fever, and euphoria.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

OVERDOSAGE

In the management of overdose with any drug, it should be borne in mind that multiple agents may have been taken.

Symptoms

Overdosage of benzodiazepines is usually manifested by varying degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy. In more serious cases, and especially when other drugs or alcohol were ingested, symptoms may include ataxia, hypotonia, hypotension, hypnotic state, stage one (1) to three (3) coma, and very rarely, death.

Management

Induced vomiting and/or gastric lavage should be undertaken, followed by general supportive care, monitoring of vital signs, and close observation of the patient. Hypotension, though unlikely, usually may be controlled with norepinephrine bitartrate injection. The value of dialysis has not been adequately determined for oxazepam.

The benzodiazepine antagonist flumazenil may be used in hospitalized patients as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose. The complete flumazenil package insert including "CONTRAINDICATIONS," "WARNINGS," and "PRECAUTIONS" should be consulted prior to use.

DOSAGE AND ADMINISTRATION

Because of the flexibility of this product and the range of emotional disturbances responsive to it, dosage should be individualized for maximum beneficial effects.

Usual Dose

Mild-to-moderate anxiety, with associated tension, irritability, agitation, or related symptoms of functional origin or secondary to organic disease.	10 to 15 mg, 3 or 4 times daily
Severe anxiety syndromes, agitation, or anxiety associated with depression.	15 to 30 mg, 3 or 4 times daily
Older patients with anxiety, tension, irritability, and agitation.	Initial dosage: 10 mg, 3 times daily. If necessary, increase cautiously to 15 mg, 3 or 4 times daily.
Alcoholics with acute inebriation, tremulousness, or anxiety on withdrawal.	15 to 30 mg, 3 or 4 times daily

This product is not indicated in pediatric patients under 6 years of age. Absolute dosage for pediatric patients 6 to 12 years of age is not established.

HOW SUPPLIED

Serax® (oxazepam) Capsules and Tablets are available in the following dosage strengths:

10 mg, NDC 63857-327-10, white and pink capsule marked "SERAX", "10", and "327", in bottles of 100 capsules.

15 mg, NDC 63857-328-10, white and red capsule marked "SERAX", "15", and "328", in bottles of 100 capsules.

30 mg, NDC 63857-329-10, white and maroon capsule marked "SERAX", "30", and "329", in bottles of 100 capsules.

15 mg, NDC 63857-332-10, yellow, five-sided, flat-faced, beveled edge tablet with a raised "S" on one side and "SERAX" and "15" on the other side, in bottles of 100 tablets.

Store at room temperature, approximately 25° C (77° F).

Keep tightly closed.

Dispense in tight container.

Reference

1. FOX, K.A.; LAHCEN, R.B.: Liver-cell Adenomas and Peliosis Hepatis in Mice Associated with Oxazepam. Res. Commun. Chem. Pathol. Pharmacol. 8:481-488, 1974.

Rx only

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