

OXAZEPAM- oxazepam capsule, gelatin coated
Aphena Pharma Solutions - Tennessee, LLC

OXAZEPAM CAPSULES, USP

CIV

40-9188

Revised — March 2012

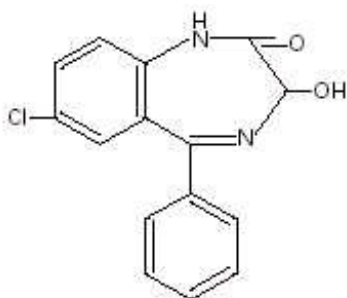
Rx only

DESCRIPTION

Oxazepam 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.

Oxazepam capsules contain 10 mg, 15 mg or 30 mg oxazepam. The following inactive ingredients are contained in these capsules: corn starch, croscarmellose sodium, FD&C Red #40, gelatin, hypromellose, lactose (monohydrate), magnesium stearate, methylparaben, propylparaben, sodium lauryl sulfate, titanium dioxide, and other inert ingredients. The 10 mg capsule also contains D&C Red #28. The 15 mg capsule also contains D&C Yellow #10. The 30 mg capsule also contains D&C Red #28 and FD&C Blue #1.

Oxazepam is 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one. A white crystalline powder with a molecular weight of 286.72, its structural formula is as follows:



CLINICAL PHARMACOLOGY

Pharmacokinetic testing in healthy adult subjects has demonstrated that a single 30 mg dose of a capsule or tablet will result in equivalent extent of absorption. Peak plasma levels 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).

INDICATIONS AND USAGE

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 Oxazepam 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 Oxazepam 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 Oxazepam, possibly requiring adjustment of dosage or elimination of such agents.

Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines (see DRUG ABUSE AND DEPENDENCE section).

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. Oxazepam, 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 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.

Information for Patients

To assure the safe and effective use of 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 oxazepam 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 oxazepam (e.g., sedation, hypotension, paradoxical excitation) cannot be ruled out (see PRECAUTIONS, General; see ADVERSE REACTIONS). In general, dose selection for oxazepam 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.

DRUG ABUSE AND DEPENDENCE

Oxazepam Capsules are classified by the Drug Enforcement Administration as a schedule IV controlled substance.

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.

OVERDOSAGE

In the management of overdosage 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

Repackaged by Aphena Pharma Solutions - TN.
See **Repackaging Information** for available configurations.



Oxazepam capsules are available as follows:

10 mg — Each pink opaque gelatin #4 capsule printed with \mathcal{P} and 067 in black ink on both cap and body contains 10 mg of Oxazepam, USP. Capsules are supplied in bottles of 100 (NDC 0228-2067-10) and 500 (NDC 0228-2067-50).

15 mg — Each red opaque gelatin #4 capsule printed with \mathcal{P} and 069 in black ink on both cap and body contains 15 mg of Oxazepam, USP. Capsules are supplied in bottles of 100 (NDC 0228-2069-10) and 500 (NDC 0228-2069-50).

30 mg — Each maroon opaque gelatin #4 capsule printed with \mathcal{P} and 073 in blue ink on both cap and body contains 30 mg of Oxazepam, USP. Capsules are supplied in bottles of 100 (NDC 0228-2073-10).

Keep tightly closed.

Dispense in a tight, light-resistant container as defined in the USP.

Store at 25(C (77(F); excursions permitted to 15(to 30(C (59(to 86(F).

ANIMAL PHARMACOLOGY AND/OR ANIMAL TOXICOLOGY

In mice, oxazepam 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 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 oxazepam 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.

REFERENCES

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.

Manufactured by:

Actavis Elizabeth LLC

200 Elmora Avenue, Elizabeth, NJ 07207 USA

40-9188

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Repackaging Information

Please reference the **How Supplied** section listed above for a description of individual tablets or capsules. This drug product has been received by Aphenia Pharma - TN in a manufacturer or distributor packaged configuration and repackaged in full compliance with all applicable cGMP regulations. The package configurations available from Aphenia are listed below:

Count	10mg	15mg
30	67544-117-30	67544-268-30
60	67544-117-53	67544-268-53
90	67544-117-60	67544-268-60
120	67544-117-70	67544-268-70

Store between 20°-25°C (68°-77°F). See USP Controlled Room Temperature. Dispense in a tight light-resistant container as defined by USP. Keep this and all drugs out of the reach of children.

Repackaged by:



Cookeville, TN 38506

20140331SC

PRINCIPAL DISPLAY PANEL - 10mg

NDC 67544-117 - **Oxazepam** 10mg - Rx Only

PRINCIPAL DISPLAY PANEL - 15mg

NDC 67544-268 - **Oxazepam** 15mg - Rx Only

OXAZEPAM

oxazepam capsule, gelatin coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:67544-117(NDC:0228-2067)
Route of Administration	ORAL	DEA Schedule	CIV

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
OXAZEPAM (UNII: 6GOW6DWN2A) (OXAZEPAM - UNII:6GOW6DWN2A)	OXAZEPAM	10 mg

Inactive Ingredients

Ingredient Name	Strength
STARCH, CORN (UNII: O8232NY3SJ)	
CROSCARMELOSE SODIUM (UNII: M28OL1HH48)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
METHYL PARABEN (UNII: A2I8C7HI9T)	
PROPYL PARABEN (UNII: Z8IX2SC1OH)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
D&C RED NO. 28 (UNII: 767IP0Y5NH)	

Product Characteristics

Color	PINK	Score	no score
Shape	CAPSULE	Size	14mm
Flavor		Imprint Code	R;067
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:67544-117-30	30 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	02/01/2007	
2	NDC:67544-117-53	60 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	01/18/2007	
3	NDC:67544-117-60	90 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	01/22/2007	
4	NDC:67544-117-70	120 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	02/27/2007	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA072251	01/02/2007	

OXAZEPAM

oxazepam capsule, gelatin coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:67544- 268(NDC:0228-2069)
Route of Administration	ORAL	DEA Schedule	CIV

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
OXAZEPAM (UNII: 6GOW6DWN2A) (OXAZEPAM - UNII:6GOW6DWN2A)	OXAZEPAM	15 mg

Inactive Ingredients

Ingredient Name	Strength
STARCH, CORN (UNII: O8232NY3SJ)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
METHYLPARABEN (UNII: A2I8C7HI9T)	
PROPYLPARABEN (UNII: Z8IX2SC1OH)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	

Product Characteristics

Color	RED	Score	no score
Shape	CAPSULE	Size	14mm
Flavor		Imprint Code	R;069
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:67544-268-30	30 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	02/20/2007	
2	NDC:67544-268-53	60 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	01/26/2007	
3	NDC:67544-268-60	90 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	01/23/2007	
4	NDC:67544-268-70	120 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	05/25/2007	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA072252	01/02/2007	

Labeler - Aphenia Pharma Solutions - Tennessee, LLC (128385585)

Establishment

Name	Address	ID/FEI	Business Operations
Aphenia Pharma Solutions - Tennessee, LLC		128385585	Repack(67544-117, 67544-268)

Revised: 12/2019

Aphenia Pharma Solutions - Tennessee, LLC