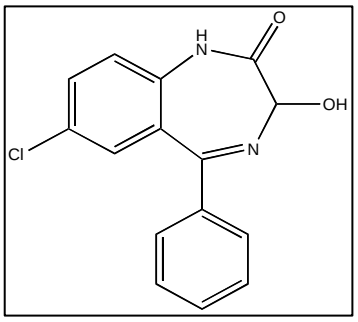
PRODUCT INFORMATION

APO-OXAZEPAM (Oxazepam) Oral

DESCRIPTION

Oxazepam (APO-OXAZEPAM), an antianxiety agent, is a 1,4 benzodiazepine with the chemical name 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepine-2-one. Oxazepam (CAS-604-75-1) has the following structural formula:



Oxazepam is a creamy-white to pale-yellow powder that is practically odourless. It is almost insoluble in water and slightly soluble in alcohol and chloroform. It has a bitter taste. The molecular weight is 286.7.

Excipients:

APO-OXAZEPAM tablets contain the following excipients: magnesium stearate, methylcellulose, polacrilin potassium and lactose

PHARMACOLOGY

The exact mechanism of action of benzodiazepines has not yet been elucidated; however, benzodiazepines appear to work through several mechanisms. Benzodiazepines presumably exert their effects by binding to specific receptors at several sites within the central nervous system either by potentiating the effects of synaptic or pre-synaptic inhibition mediated by gamma-aminobutyric acid or by directly affecting the action potential generating mechanisms.

APO-OXAZEPAM is readily absorbed when given orally. Peak concentrations in plasma occur approximately 2-3 hours following administration of 30 mg. The half-life of oxazepam in human plasma ranges from 4 to 15 hours. At clinically relevant concentrations, oxazepam is 95% to 98% bound to plasma protein. Oxazepam is conjugated at its 3-hydroxy substituent to its glucuronide, which accounts for at least 95% of the urinary excretion products. There are no active metabolites of oxazepam. Multiple-dose therapy leads to no excessive drug accumulation.

There is no indication of induction of drug-metabolising enzymes with oxazepam. Oxazepam is not a substrate for N-dealkylating enzymes of the cytochrome P450 system nor is it hydroxylated to any significant extent.

The pharmacokinetics of oxazepam remain unaltered in older patients, however the elderly generally show increased central nervous system sensitivity to benzodiazepines, and may require a reduced dosage. Hepatic diseases (hepatitis, alcoholic cirrhosis) have a minimal influence on oxazepam kinetics, however these patients have increased cerebral sensitivity to benzodiazepines and dosage reduction may be advisable. As with other benzodiazepines, the pharmacokinetics of oxazepam may change in patients with impaired renal function and the medication should be used with caution.

INDICATIONS

APO-OXAZEPAM is indicated for:

1. Management of anxiety disorders or for the short-term relief of the symptoms of anxiety. Anxiety associated with depression is also responsive to APO-OXAZEPAM therapy. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. The physician should periodically reassess the usefulness of the drug for the individual patient.

2. Alcoholics with acute tremulousness, confusional state or anxiety associated with alcohol withdrawal are responsive to therapy.

CONTRAINDICATIONS

APO-OXAZEPAM is contraindicated in:

1. Patients with known hypersensitivity to benzodiazepines.
2. Patients with chronic obstructive airways disease with incipient respiratory failure.
3. Patients with sleep apnoea.

PRECAUTIONS

1. As with all patients taking CNS-depressant medications, patients receiving APO-OXAZEPAM should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from APO-OXAZEPAM therapy. Abilities may be impaired on the day following use. Patients should be advised that their tolerance for alcohol and other CNS depressants will be diminished and that these medications should either be eliminated or given in reduced dosage in the presence of APO-OXAZEPAM.

2. Following the prolonged use of APO-OXAZEPAM at therapeutic dose withdrawal from the medication should be gradual. An individualised withdrawal timetable needs to be planned for each patient in whom dependence is known or suspected. Periods from four weeks to four months have been suggested. As with other benzodiazepines, when treatment is suddenly withdrawn, a temporary increase of sleep disturbance can occur after use of APO-OXAZEPAM (see Dependence).

3. In general, benzodiazepines should be prescribed for short periods only (e.g. 2-4 weeks). Continuous long-term use of APO-OXAZEPAM is not recommended. There is evidence that tolerance develops to the sedative effects of benzodiazepines. After as little as one week of therapy withdrawal symptoms can appear following the cessation of recommended doses (eg rebound insomnia following cessation of a hypnotic benzodiazepine).

4. Although hypotension has occurred only rarely, APO-OXAZEPAM should be administered with caution to patients in whom a drop in blood pressure might lead to cardiac or cerebral complications. This is particularly important in elderly patients.

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

6. APO-OXAZEPAM could increase the muscle weakness in myasthenia gravis and should be used with caution in this condition.

7. Caution should be used in the treatment of patients with narrow-angle glaucoma (because of atropine-like side effects).

8. Impaired Renal/Liver Function and Blood Dyscrasias: Patients with impaired renal or hepatic function should use benzodiazepine medication with caution and dosage reduction may be advisable. In rare instances some patients taking benzodiazepines have developed blood dyscrasias, and some have had elevations of liver enzymes. As with other benzodiazepines, periodic blood counts and liver function tests are recommended.

9. Depression, Psychosis and Schizophrenia: APO-OXAZEPAM is not recommended as primary therapy in-patients with depression and psychosis. In such conditions, psychiatric assessment and supervision are necessary if benzodiazepines are indicated. Benzodiazepines may increase depression in some patients, and may contribute to deterioration in severely disturbed schizophrenics with confusion and withdrawal. Suicidal tendencies may be present or uncovered and protective measures may be required.

10. Paradoxical reactions such as acute rage, stimulation or excitement may occur; should such reactions occur, APO-OXAZEPAM should be discontinued.

11. Geriatric or debilitated patients: Such patients may be particularly susceptible to the sedative effects of benzodiazepines and associated giddiness, ataxia and confusion, which may increase the possibility of a fall.

12. Impaired Respiratory Function: Caution in the use of APO-OXAZEPAM is recommended in-patients with respiratory depression. In-patients with chronic obstructive pulmonary disease, benzodiazepines can cause increased arterial carbon dioxide tension and decreased arterial oxygen tension.

13. Epilepsy: Abrupt withdrawal of benzodiazepines in-patients with convulsive disorders may be associated with a temporary increase in the frequency and/or severity of seizures.

14. ABUSE: Caution must be exercised in administering APO-OXAZEPAM to individuals known to be addiction prone or those whose history suggests they may increase the dosage on their own initiative. It is desirable to limit repeat prescription without adequate medical supervision.

15. DEPENDENCE: The use of benzodiazepines may lead to dependence as defined by the presence of a withdrawal syndrome on discontinuation of the drug. Tolerance as defined by a need to increase the dose in order to achieve the same therapeutic effect seldom occurs in-patients receiving recommended doses under medical supervision.

Tolerance to sedation may occur with benzodiazepines especially in those with drug seeking behaviour. Withdrawal symptoms similar in character to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of benzodiazepines. These symptoms can range from insomnia, anxiety, dysphoria, palpitations, panic attacks, vertigo, myoclonus akinesia, hypersensitivity to light, sound and touch, abnormal body sensations (eg feelings of motion, metallic taste), depersonalisation, derealisation, delusional beliefs, hyperreflexia and loss of short term memory, to a major syndrome which may include convulsions, tremor, abdominal and muscle cramps, confusional states, delirium, hallucinations, hyperthermia, psychosis, vomiting and sweating. Such manifestations of withdrawal, especially the more serious ones, are more common in those patients who have received excessive doses over a prolonged period. However, withdrawal symptoms have also been reported following abrupt discontinuation of benzodiazepines taken continuously at therapeutic levels. Accordingly, APO-OXAZEPAM should be terminated by tapering the dose to minimise occurrence of withdrawal symptoms. Patients should be advised to consult with their physician before either increasing the dose or abruptly discontinuing the medication.

Rebound phenomena have been described in the context of benzodiazepine use. Rebound insomnia and anxiety mean an increase in the severity of these symptoms beyond pre-treatment levels following cessation of benzodiazepines. Rebound phenomena in general possibly reflect re-emergence of pre-existing symptoms combined with withdrawal symptoms described earlier. Some patients prescribed benzodiazepines with very short half-lives (in the order of 2 to 4 hours) may experience relatively mild rebound symptoms in between their regular doses. Withdrawal/rebound symptoms may follow high doses taken for relatively short periods.

Carcinogenicity / Mutagenicity and Impairment of Fertility: In a two-year carcinogenicity study in which rats were administered oxazepam in the diet (5,15,60 mg/kg/day), no oxazepam-related malignant tumours were found. However, there was a significant increase in the incidence of testicular interstitial cell tumours and thyroid cystadenomas (benign tumours) in high-dose males. There was also a significant trend for increased incidence of prostatic adenomas. An earlier published study reported that mice fed diets containing 0.05% or 0.15% oxazepam for nine months developed a dose-related increase in liver adenomas. In an independent analysis of some of the microscopic slides from this mouse study several of these tumours were classified as liver carcinomas. Although comprehensive studies have not been performed to examine the possibility of an increased incidence of tumours in humans exposed to oxazepam, at the present time there is no evidence that the clinical use of oxazepam is associated with tumours.

In-vitro mutagenicity reports on oxazepam are inconclusive. One study reported oxazepam to be mutagenic in a modified Ames *Salmonellae typhimurium* test in the presence, but not in the absence, of metabolic activation. Other investigations (employing the Salmonella/microsome test, the Ames test, and tests in *Aspergillus nidulans*, *Saccharomyces cerevisiae*, isolated rat hepatocytes and a rat liver cell line) have obtained negative results for the mutagenicity of oxazepam.

Impairment of Fertility - Female mice fed diets containing 0.05% or 0.75% oxazepam were reported to exhibit significant decreases in the frequency of vaginal oestrus.

USE DURING PREGNANCY: **Category C.**
Benzodiazepines cross the placenta and may cause hypotonia, reduced respiratory function and hypothermia in the newborn infant. Continuous treatment during pregnancy and administration of high doses in connection with delivery should be avoided. Withdrawal symptoms in newborn infants have been reported with this class of drugs.
The use, of benzodiazepines during the first trimester of pregnancy should almost always be avoided. If the drug is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuation of the drug if she intends to become or suspects that she is pregnant.

Non-Teratogenic Effects - The use of benzodiazepines during the last phase of pregnancy or at delivery may require ventilation of the infant at birth.

Australian categorisation definition of Category C
Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.

USE DURING LACTATION
Caution should be exercised when APO-OXAZEPAM is given to a breast-feeding woman. Oxazepam is excreted in human breast milk and may cause drowsiness and feeding difficulties in the infant.

Paediatric Use: The safety and effectiveness of oxazepam has not been established in children less than 16 years of age.

INTERACTIONS WITH OTHER DRUGS

1. The benzodiazepines, including oxazepam, produce additive CNS depressant effects when co-administered with other medications which themselves produce CNS depression, e.g. barbiturates, alcohol, sedatives, tricyclic antidepressants, non selective MAO inhibitors, phenothiazines and other antipsychotics, skeletal muscle relaxants, antihistamines or narcotic analgesics and anaesthetics.

2. The cytochrome P450 system has not been shown to be involved in the disposition of oxazepam and, unlike many benzodiazepines, pharmacokinetic interactions involving the P450 system have not been observed with oxazepam.

3. The anticholinergic effects of other drugs, including atropine and similar drugs, antihistamines and antidepressants may be potentiated.

4. Interactions have been reported between some benzodiazepines and anticonvulsants, with changes in the serum concentration of the benzodiazepine or anticonvulsant. It is recommended that patients be observed for altered responses when benzodiazepines and anticonvulsants are prescribed together, and that serum level monitoring of the anticonvulsant be performed more frequently.

5. Minor EEG changes, usually low voltage fast activity, of no known clinical significance; have been reported with benzodiazepine administration.

INTERFERENCE WITH CLINICAL, LABORATORY AND OTHER TESTS

1. Oxazepam may decrease values of leukocytes in testing for leukopoiesis.
2. Oxazepam may give high blood glucose level utilising the Somogyi procedure but not the glucose oxidase procedure.

ADVERSE REACTIONS

More Common Reactions

Mild drowsiness, if it occurs, is usually observed at the beginning of therapy and generally decreases in severity or disappears on continued medication or upon decreasing the dose.

Less Common Reactions

Cardiovascular:	oedema, hypotension.
Dermatological:	skin rashes (morbilliform, urticarial and maculopapular).
Gastrointestinal:	nausea, hepatic dysfunction, and abdominal pain.
General:	hypersensitivity, lethargy, altered libido, slurred speech, blurred vision, disorientation and fever.
Haematological:	leucopenia.
Musculo-Skeletal:	tremor, paraesthesia.
Nervous System:	dizziness, vertigo, headache, syncope, ataxia, confusion, hallucination, aggression, and unpleasant dreams.
Psychiatric:	paradoxical reactions.

Paradoxical reactions such as stimulation, excitement, or rage rarely occur (see PRECAUTIONS).

Serious or Life Threatening Reactions

Although rare, leucopenia and hepatic dysfunction including jaundice have been reported during oxazepam therapy.

DOSAGE AND ADMINISTRATION

APO-OXAZEPAM is administered orally. For optimal results, dose, frequency of administration, and duration of therapy should be individualised according to patient response.

For mild to moderate anxiety, with associated tension, irritability, agitation or related symptoms of functional origin or secondary to organic disease, the usual dose is 7.5-15 mg, 3 or 4 times daily.

For severe anxiety syndromes, agitation or anxiety associated with depression, the usual dose is 15-30 mg, 3 or 4 times daily.

For older patients with anxiety, tension, irritability and agitation, the initial dose is 7.5 mg, 2-3 times daily. If necessary, increase cautiously to 15 mg, 3 or 4 times daily.

For alcoholics with tremulousness or anxiety on withdrawal, the usual dose is 15-30 mg, 3 or 4 times daily. APO-OXAZEPAM should not be administered to alcoholics with acute inebriation.

Paediatric Use - APO-OXAZEPAM is not indicated in children under 16 years of age.

The need for continued therapy with APO-OXAZEPAM in-patients who have been taking medication for several weeks should be evaluated periodically.

OVERDOSAGE

Overdose of benzodiazepines is usually manifested by 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, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, coma, and very rarely proves fatal.

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

Following overdose with oral benzodiazepines, activated charcoal should be given to reduce absorption. Hypotension and respiratory depression should be managed according to general principles.

Haemoperfusion and haemodialysis are not useful in benzodiazepine intoxication. The benzodiazepine antagonist flumazenil may be used in hospitalised patients for the reversal of acute benzodiazepine effects. Please consult the flumazenil product information prior to usage.

PRESENTATION

Tablets: 30 mg (white, round tablet, one face convex embossed “30”, opposite face flat with Ezi-split breakline), 25's

To break tablet, place on hard surface with score facing upwards and press gently on tablet with thumb.

POISON SCHEDULE: S4.

STORAGE: Store below 30^{o}C.

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