

1 NAME OF THE MEDICINE

Oxazepam

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ALEPAM 15 and ALEPAM 30 tablet contains 15 mg and 30 mg of oxazepam, respectively.

Excipients with known effect: sugars as lactose and trace quantities of sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

ALEPAM 15 (oxazepam) 15 mg: 8 mm pale yellow flat bevelled edged tablet marked OM/15 on one side, G on reverse.

ALEPAM 30 (oxazepam) 30 mg: 8 mm pale orange flat bevelled edged tablet marked OM/30 on one side, G on reverse.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ALEPAM is indicated for:

- Management of anxiety disorders or for the short-term relief of the symptoms of anxiety. Anxiety associated with depression is also responsive to 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.
- Alcoholics with acute tremulousness, confusional state or anxiety associated with alcohol withdrawal are responsive to therapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

ALEPAM 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 to 15 mg, 3 or 4 times daily.

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

For older patients with anxiety, tension, irritability and agitation, the initial dose is 7.5 mg, 2 to 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 to 30 mg, 3 or 4 times daily. ALEPAM should not be administered to alcoholics with acute inebriation.

Paediatric Use. ALEPAM is not indicated for use in children under 16 years of age.

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

4.3 CONTRAINDICATIONS

ALEPAM is contraindicated in:

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with all patients taking CNS-depressant medications, patients receiving ALEPAM should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from ALEPAM 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 ALEPAM.

Following the prolonged use of ALEPAM at therapeutic doses, 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 ALEPAM (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Dependence).

In general, benzodiazepines should be prescribed for short periods only (e.g. 2 to 4 weeks). Continuous long-term use of ALEPAM 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 (e.g. rebound insomnia following cessation of a hypnotic benzodiazepine).

Although hypotension has occurred only rarely, ALEPAM 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.

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

Oxazepam could increase the muscle weakness in myasthenia gravis and should be used with caution in this condition.

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

Blood Dyscrasias

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.

Depression, Psychosis and Schizophrenia

ALEPAM 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.

Paradoxical Reactions

Paradoxical reactions such as acute rage, stimulation or excitement may occur; should such reactions occur, ALEPAM should be discontinued.

Impaired Respiratory Function

Caution in the use of ALEPAM 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.

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.

Abuse

Caution must be exercised in administering ALEPAM 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.

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 (e.g. 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, ALEPAM 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.

Use in Hepatic Impairment

Patients with impaired 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.

Use in Renal Impairment

Patients with impaired renal function should use benzodiazepine medication with caution and dosage reduction may be advisable.

Use in the Elderly

Elderly or debilitated 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.

Paediatric Use

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

Excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or galactose malabsorption should not take this medicine.

Effects on Laboratory Tests

Oxazepam may decrease values of leucocytes in testing for leucopoiesis.

Oxazepam may give high blood glucose level utilising the Somogyi procedure but not the glucose oxidase procedure.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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, nonselective MAO inhibitors, phenothiazines and other antipsychotics, skeletal muscle relaxants, antihistamines or narcotic analgesics and anaesthetics.

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.

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

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.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

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 in Pregnancy

Category C

Benzodiazepines cross the placenta and may cause hypotonia, respiratory depression 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 child-bearing 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.

Use in Lactation

Caution should be exercised when ALEPAM is given to a breastfeeding woman. ALEPAM is excreted in

human breast milk, and may cause drowsiness and feeding difficulties in the infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

As with all patients taking CNS-depressant medications, patients receiving ALEPAM should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from ALEPAM 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 ALEPAM.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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, 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, unpleasant dreams.

Psychiatric

Paradoxical reactions. Paradoxical reactions such as stimulation, excitement, or rage rarely occur (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Serious or Life-Threatening Reactions

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

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

Overdosage 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 overdosage with any medication, it should be borne in mind that multiple agents may have been taken.

Following overdosage with oral benzodiazepines, vomiting should be induced (within one hour) if the patient is conscious, or gastric lavage undertaken with the airways protected if the patient is comatose. If there is no advantage in emptying the stomach, 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Oxazepam is an anti-anxiety agent which belongs to the benzodiazepine class of drugs.

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.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Oxazepam is readily absorbed when given orally. Peak concentrations in plasma occur approximately 2 to 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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

In-vitro mutagenicity reports on oxazepam are inconclusive. One study reported oxazepam to be mutagenic in a modified Ames Salmonella 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.

Carcinogenicity

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets also contain the following inactive ingredients: lactose monohydrate, maize starch, quinoline yellow aluminium lake, erythrosine aluminium lake, magnesium stearate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

ALEPAM 15: HDPE bottles with PP child resistant closures and PVC/PVDC/Al blister packs of 25, 50, 90, 1000s

ALEPAM 30: HDPE bottles with PP child resistant closures and PVC/PVDC/Al blister packs of 25, 50, 90, 1000s

Some pack sizes may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 17572 - ALEPAM 15 oxazepam 15 mg tablet bottle

AUST R 17573 - ALEPAM 30 oxazepam 30 mg tablet bottle

AUST R 385081 - ALEPAM 15 oxazepam 15 mg tablet blister pack

AUST R 385082 - ALEPAM 30 oxazepam 30 mg tablet blister pack

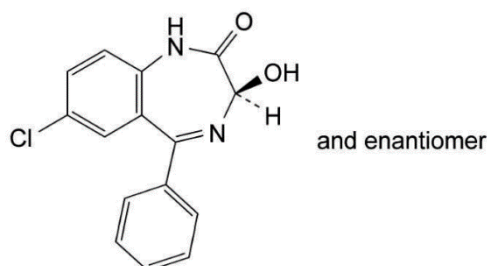
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

A white or almost white, crystalline powder, practically insoluble in water, slightly soluble in alcohol and in methylene chloride.

Chemical Structure



Chemical name: (3*RS*)-7-chloro-3-hydroxy-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one

Molecular formula: C₁₅H₁₁ClN₂O₂

Molecular weight: 286.72

CAS Number

604-75-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

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Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

20/09/1991

10 DATE OF REVISION

18/04/2023

Summary Table of Changes

Section Changed	Summary of New Information
6.1	Update of excipient name