AUSTRALIAN PRODUCT INFORMATION

KALMA®

(alprazolam) tablet

1 NAME OF THE MEDICINE

Alprazolam

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

KALMA tablets contain alprazolam, an anti-anxiety, benzodiazepine derivative chemically and pharmacologically related to other drugs of this class.

Each KALMA 0.25 tablet contains 0.25 mg of alprazolam; each KALMA 0.5 tablet contains 0.5 mg of alprazolam; each KALMA 1 tablet contains 1 mg of alprazolam; each KALMA 2 tablet contains 2 mg of alprazolam.

Excipients with known effect: sugars as lactose, benzoates and sulfites.

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

3 PHARMACEUTICAL FORM

KALMA 0.25 mg tablet: 9mm x 5.5mm oval, white tablet debossed AL | 0.25 on one side, G on the reverse.

KALMA 0.5 mg tablet: 9mm x 5.5mm oval, pale pink tablet, debossed AL | 0.5 on one side, G on the reverse.

KALMA 1 mg tablet: 9mm x 5.5mm oval, pale blue tablet, debossed AL | 1.0 on one side, G on the reverse.

KALMA 2 mg tablet: 9.5 mm x 9.0 mm white oval bevel edged quadrisect tablet marked "A" in the upper left quadrant "L" in the upper right quadrant "G" in the lower left quadrant, "2" in the lower right quadrant on one side, plain quadrisect on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Anxiety

Short-term symptomatic treatment of anxiety including treatment of anxious patients with some symptoms of depression.

Panic disorder

The treatment of panic disorder with or without some phobic avoidance, and for blocking or attenuation of panic attacks and phobias in patients who have agoraphobia with panic attacks.

The diagnostic criteria for panic disorder in DSM-III-R are as follows:

The panic attacks (discrete periods of intense fear or discomfort), at least initially, are unexpected. Later in the course of this disturbance, certain situations (e.g. driving a car or being in a crowded place) may become associated with having a panic attack. These panic attacks are not triggered by situations in which the person is the focus of others' attention (as in social phobia).

The diagnosis requires four such attacks within a four week period, or one or more attacks followed by at least a month of persistent fear of having another attack.

The panic attacks must be characterised by at least four of the following symptoms: dyspnoea or smothering sensations; dizziness, unsteady feelings or faintness; palpitations or tachycardia; trembling or shaking;

sweating; choking; nausea or abdominal distress; depersonalisation or derealisation; paraesthesiae; flushes (hot flashes) or chills; chest pain or discomfort; fear of dying; fear of going crazy or of doing something uncontrolled.

Note. Attacks involving four or more symptoms are panic attacks; attacks involving fewer than four are limited symptom attacks.

At least some of the panic attack symptoms must develop suddenly and increase in intensity within ten minutes of the beginning of the first symptom noticed in the attack.

The panic attack must not be attributable to some known organic factor, e.g. amphetamine or caffeine, intoxication, hyperthyroidism.

The efficacy of alprazolam in conditions where the above criteria are not met has not been established. The risk versus benefits of alprazolam use in milder disorders, which do not meet the above criteria, has not been evaluated. Although current evidence supports the long-term clinical effectiveness of alprazolam in panic disorder, the continuing use of alprazolam needs to be weighed against the difficulties that can occur with dependence and discontinuation.

The results of a long-term study in patients taking alprazolam (ie. beyond three months) suggest that many patients continue to benefit from alprazolam therapy and that alprazolam efficacy is maintained for up to eight months.

The physician should periodically reassess the usefulness of the drug for each patient.

A comparative study of alprazolam and placebo in the treatment of panic attacks in patients with panic disorder involved 543 patients over an eight week period. Alprazolam was significantly more effective than placebo in reducing the total number of panic attacks ($p < 0.0001$); at week 4, 46.8% of alprazolam patients had achieved zero total panic attacks when compared to 27.1% of placebo patients.

Panic disorders are often severe, chronic illnesses that cause a high level of work and social disability, increased substance abuse and potentially increased morbidity and mortality.

Psychological and social factors are important in the pathogenesis of panic attacks, either acting alone or in combination with biological factors. Prolonged pharmacological therapy may be used as an adjunct to psychosocial therapy in the treatment of patients with panic disorders.

4.2 DOSE AND METHOD OF ADMINISTRATION

The optimum dosage of KALMA should be individualised, based upon the severity of the symptoms and individual patient response. The daily dosage shown in Table 1 will meet the needs of most patients. In the few patients who require higher doses, dosage should be increased cautiously to avoid adverse effects. When higher dosage is required, the evening dose should be increased before the daytime doses. In general, patients who have not previously received psychotropic medication will require lower doses than those previously treated with minor tranquillizers, antidepressants, or hypnotics or those with a history of chronic alcoholism. It is recommended that the general principle of using the lowest effective dosage be followed to preclude the development of oversedation or ataxia.

In patients who experience early morning anxiety and emergence of anxiety symptoms, it is recommended that the same total daily dose be given divided as more frequent administration.

Patients should be periodically reassessed and dosage adjustments made, as appropriate.

Table 1 KALMA - Recommended Dosage Schedule

Condition	Usual starting dosage*	Usual dosage range
Anxiety	0.5 to 1.5 mg daily, given in divided doses.	0.5 to 4 mg daily, given in divided doses
*Anxiety with depressive symptoms	1.5 mg daily, given in divided doses	1.5 to 4.5 mg daily, given in divided doses
Elderly patients or in the presence of debilitating disease	0.5 to 0.75 mg daily, given in divided doses	0.5 to 0.75 mg daily, given in divided doses; to be gradually increased if needed and tolerated
Panic related disorders	0.5 to 1.0 mg, given at bedtime, increasing at a rate of 0.25 to 1 mg every 3 days until an adequate therapeutic dosage is achieved.	The dose should be adjusted to patient response. Dosage adjustments should be in increments not greater than 1 mg every 3 to 4 days. Additional doses can be added until a 3 or 4 times daily schedule is achieved. The mean dose in a large multiclinic study was 5.7 ± 2.27 mg with rare patients requiring a maximum of 10 mg daily.

* If side effects occur, the dose should be lowered.

Administration of KALMA immediately after meals does not affect the extent of absorption compared to administration on an empty stomach. Food does, however, delay the onset of absorption and decrease the rate of absorption of alprazolam. As a direct consequence, side effects such as somnolence are less pronounced.

Discontinuation Therapy

The dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of KALMA be decreased by 0.25 to 0.5 mg every three days. It is important that this rate of dosage reduction does not exceed 0.5 mg every three days in order to minimise any possible withdrawal symptoms. Some patients may require an even slower dosage reduction (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.3 CONTRAINDICATIONS

KALMA is contraindicated in:

- Known hypersensitivity to benzodiazepines, alprazolam, or to any component of these products' formulations.
- Chronic obstructive airways disease with incipient respiratory failure.
- Myasthenia gravis.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required.

Identified Precautions

Depression, Psychosis and Schizophrenia

Alprazolam 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.

Panic related disorders have been associated with depression and an increased frequency of suicide amongst untreated patients has been reported. Therefore, the precautions exercised when using any psychotropic drug in depressed patients or potentially suicidal patients should be applied when using higher doses of alprazolam in patients with panic related disorders Episodes of hypomania and mania have been reported in association with the use of alprazolam in patients with depression.

Psychiatric and Paradoxical Reactions

In many of the spontaneous case reports of adverse behavioural effects, patients were receiving other CNS drugs concomitantly and/or were described as having underlying psychiatric conditions. Patients who have borderline personality disorder, a prior history of violent or aggressive behaviour, or alcohol or substance abuse may be at risk for such events.

Paradoxical reactions such as acute rage, stimulation or excitement may occur in rare instances; should such reactions occur, KALMA should be discontinued.

Hypotension

Although hypotension has occurred only rarely, KALMA 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.

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.

Patients with convulsive disorders should not be abruptly withdrawn from KALMA.

Impaired Respiratory Function

Caution in the use of alprazolam is recommended in patients with respiratory depression. In patients with chronic obstructive pulmonary disease, benzodiazepines can cause increased arterial carbon dioxide tension and decreased oxygen tension.

Acute Narrow-Angle Glaucoma

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

Amnesia

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

Abuse

Physical and psychological dependence have occurred with recommended doses of benzodiazepines. As with all benzodiazepines, the risk of dependence increases with higher doses and long-term use and is further increased in patients with a history of alcoholism or drug abuse. Caution must therefore be exercised in administering KALMA to individuals known to be addiction prone or those whose history suggests they may increase the dosage on their own initiative. Alprazolam may be subject to diversion. There have been reports of overdose-related deaths when alprazolam is abused with other central nervous system (CNS) depressants including opioids, other benzodiazepines, and alcohol. In such patients it is therefore desirable to limit repeat prescription without adequate medical supervision. Such individuals should be under careful surveillance when receiving benzodiazepines because of their predisposition to habituation and dependence.

Withdrawal and 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.

The result of withdrawal symptoms is a direct consequence of physical dependence to KALMA tablets. Signs and symptoms of withdrawal are similar in character to those noted with barbiturates and alcohol and are more prominent after a rapid decrease of dosage or abrupt discontinuation. These symptoms 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 patients who have received excessive doses over a prolonged period. However, withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines taken continuously at therapeutic levels.

Signs and symptoms of withdrawal are more prominent after a rapid decrease of dosage or abrupt discontinuation of benzodiazepines. Hence, abrupt discontinuation of therapy with alprazolam should be avoided. It is recommended that all patients on KALMA tablets who require a dosage reduction be gradually tapered under close supervision (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Discontinuation therapy) to minimise the incidence or severity of withdrawal problems. It is important to advise patients not to increase the dose of, or abruptly discontinue, their medication without first consulting a doctor.

The discontinuation of therapy with KALMA tablets may not only result in withdrawal symptoms, but also in relapse of the anxiety and panic symptoms of the original disorder and a rebound effect. The term relapse refers to the return of symptoms characteristic of the original disorder, at levels approximately equal to those seen at baseline before active treatment was initiated. Rebound phenomena refer to the return of symptoms characteristic of the original disorder at levels greater than originally seen at baseline.

In general, rebound phenomena reflect the re-emergence of pre-existing conditions combined with withdrawal symptoms described earlier. Withdrawal/rebound phenomena may follow high doses of benzodiazepines for relatively short periods of time.

In a large database comprising both controlled and uncontrolled studies in which 641 patients received alprazolam tablets for the treatment of panic disorder, discontinuation emergent symptoms which occurred at a rate of over 5% in patients treated with alprazolam tablets and at a greater rate than the placebo treated group were as shown in Table 2.

Table 2 Discontinuation-Emergent Symptom Incidence

Percentage of alprazolam treated panic disorder patients reporting events (n = 641)

Adverse Event	%	Adverse Event	%
Nervous System		**Gastrointestinal**	
Insomnia	29.5	Nausea/vomiting	16.5
Lightheadedness	19.3	Diarrhoea	13.6
Abnormal involuntary movement	17.3	Decreased salivation	10.6
Headache	17.0		
Muscle twitching	6.9	**Metabolic/nutritional**	
Impaired coordination	6.6	Weight loss	13.3
Muscle tone disorders	5.9	Decreased appetite	12.8
Weakness	5.8		
		Dermatological	
Psychiatric	19.2	Sweating	14.4
Anxiety	18.4		
Fatigue and tiredness	10.5	**Cardiovascular**	
Irritability	10.3	Tachycardia	12.2
Cognitive disorder	5.5		
Memory impairment	5.1	**Special senses**	
Depression	5.0	Blurred vision	10.0
Confusional state			

From the studies cited, it has not been determined whether these symptoms are clearly related to the dose and duration of therapy of alprazolam tablets in patients with panic disorder.

These discontinuation emergent symptoms do not appear to differ from those associated with other benzodiazepines.

In two controlled trials of six to eight weeks duration, in which the ability of patients to discontinue medication was measured, 71 to 93% of alprazolam treated patients tapered completely off therapy compared to 89 to 96% of placebo treated patients.

In a controlled clinical trial of three to twelve months duration involving 144 patients, in which the ability of patients to discontinue medication was measured, it was found that the majority of alprazolam treated patients (66.9%) were able to taper dose to zero. A minority of patients were unable to successfully stop alprazolam after long-term therapy.

Instances of irritability, hostility and intrusive thoughts have been reported during discontinuance of alprazolam in patients with post-traumatic stress disorder.

Use in Renal and Hepatic Impairment

Patients with impaired renal or hepatic function should use benzodiazepine medication with caution and dosage reduction or a decision not to prescribe may be necessary in such patients. 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 the Elderly

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. For elderly or debilitated patients, the dosage should be limited to the smallest effective amount to preclude such effects.

Paediatric Use

The safety and efficacy of KALMA in children have not been established.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The benzodiazepines, including alprazolam, produce additive CNS depressant effects when co-administered with other medications which themselves produce CNS depression, e.g. barbiturates, opioids, alcohol, sedatives, tricyclic antidepressants, non-selective MAO inhibitors, phenothiazines and other antipsychotics, skeletal muscle relaxants, antihistamines or narcotic analgesics and anaesthetics (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Pharmacokinetic interactions can occur when alprazolam is administered along with drugs that interfere with its metabolism. Compounds which inhibit certain hepatic enzymes (particularly cytochrome P4503A4) may increase the concentration of alprazolam and enhance its activity. Data from clinical studies with alprazolam, *in vitro* studies with alprazolam, and clinical studies with drugs metabolized similarly to alprazolam provide evidence for varying degrees of interaction and possible interaction with alprazolam for a number of drugs. Based on the degree of interaction and the type of data available, the following recommendations are made:

- The coadministration of alprazolam with ketoconazole, itraconazole, or other azole antifungals is not recommended. Ketoconazole and itraconazole are potent CYP3A inhibitors and have been shown *in vivo* to increase plasma alprazolam concentrations.

- Caution and consideration of dose reduction is recommended when alprazolam is co-administered with fluvoxamine and cimetidine.

- Caution is recommended when alprazolam is coadministered with fluoxetine, propoxyphene, and oral contraceptives. Oral contraceptives may increase the elimination half-life of alprazolam; a 20% increase in the alprazolam steady-state plasma concentration may be expected in women taking alprazolam tablets and oral contraceptives concurrently.

- Caution is recommended when alprazolam is coadministered with diltiazem, isoniazid, macrolide antibiotics such as erythromycin and clarithromycin, grapefruit juice, ergotamine, cyclosporine, amiodarone, and nifedipine.

- Interactions involving HIV protease inhibitors (e.g. ritonavir) and alprazolam are complex and time dependent. Low doses of ritonavir resulted in a large impairment of alprazolam clearance, prolonged its elimination half-life and enhanced clinical effects. However, upon extended exposure to ritonavir, CYP3A induction offset this inhibition. This interaction will require a dose-adjustment or discontinuation of alprazolam.

- Increased digoxin concentrations have been reported when alprazolam was given, especially in the elderly (>65 years of age). Patients who receive alprazolam and digoxin should therefore be monitored for signs and symptoms related to digoxin toxicity.

Alprazolam may also interact with disulfiram resulting in increased plasma levels of alprazolam.

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.

The steady state plasma concentrations of imipramine and desipramine, have been reported to be increased an average of 31 and 20% respectively, by the concomitant administration of alprazolam tablets in doses up to 4 mg/day. The clinical significance of these changes is unknown.

Alprazolam causes a small decrease (7%) in lithium clearance. Caution should be exercised with the close monitoring of lithium concentrations to avoid toxicity.

Alprazolam tablets did not affect the prothrombin times or plasma warfarin levels in male volunteers administered sodium warfarin orally.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Alprazolam did not impair fertility in rats up to the highest dose tested of 5 mg/kg/day, which is 4.5 times the maximum recommended daily human dose based on body surface area comparison, assuming a body weight of 50 kg.

Animal studies with benzodiazepines have shown potential cognitive and behavioural effects following exposure during third trimester of pregnancy of unknown relevance to human use.

Use in Pregnancy

Pregnancy Category: Category C

The safety of alprazolam for use in pregnancy has not been established. Benzodiazepines can potentially cause foetal harm when administered to pregnant women. If alprazolam is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the foetus. Because of experience with other members of the benzodiazepine class, alprazolam is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. Because use of these drugs is rarely a matter of urgency, their use during the first trimester should almost always be avoided. The data concerning teratogenicity and effects in postnatal development and behaviour following benzodiazepine treatment are inconsistent. There is evidence from some early studies with other members of the benzodiazepine class that *in utero* exposure may be associated with malformations. Later studies with the benzodiazepine class of drugs have provided no clear evidence of any type of defect.

Infants exposed to benzodiazepines during the late third trimester of pregnancy or during labour have been reported to exhibit either the floppy infant syndrome or neonatal withdrawal symptoms. 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.

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 physicians about the desirability of discontinuing the drug.

Use in Lactation

Benzodiazepines, including alprazolam, are known to be excreted in human milk. Benzodiazepines generally show increased toxicity in neonates, and the excretion of benzodiazepines in breast milk may cause drowsiness, lethargy, weight loss, hypotonia and/or feeding difficulties in the infant. Therefore, KALMA is not recommended for use in breastfeeding, unless there are compelling circumstances to the contrary.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

Following the prolonged use of KALMA 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 KALMA (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Withdrawal and Dependence).

In general, benzodiazepines should be prescribed for short periods only (e.g. 2 to 4 weeks). With the exception of the use of KALMA for the treatment of panic disorder (see Section 4.1 THERAPEUTIC INDICATIONS), continuous long-term use of KALMA 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 an anxiolytic benzodiazepine (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Withdrawal and Dependence).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Side effects, if they occur, are generally observed at the beginning of therapy and usually disappear upon continued medication or decreased dosage. In patients treated for anxiety, and anxiety associated with depression, the most common adverse reactions to alprazolam were drowsiness and light headedness/dizziness. Common adverse effects include disorientation, libido decreased, balance disorder, hypersomnia, lethargy, constipation, dry mouth and nausea. Less common adverse reactions were blurred vision, headache, depression, insomnia, nervousness/ anxiety, tremor, change in weight, memory impairment/amnesia, coordination disorders, various gastrointestinal symptoms, and autonomic manifestations. As with other benzodiazepines, reactions such as stimulation, agitation, concentration difficulties, confusion, hallucinations or other adverse behavioural effects have been reported with alprazolam. Increased intraocular pressure has been rarely reported.

In addition, the following adverse events have been reported in association with the use of anxiolytic benzodiazepines including alprazolam: dystonia, irritability, anorexia, fatigue, slurred speech, jaundice, musculoskeletal weakness, changes in libido, menstrual irregularities, incontinence, urinary retention, abnormal hepatic function and hyperprolactinaemia.

The most common adverse reactions in patients with panic related disorders were sedation/drowsiness; fatigue, ataxia/impaired coordination and slurred speech. Less common adverse reactions were altered mood, gastrointestinal symptoms, dermatitis, memory problems, sexual dysfunction, intellectual impairment and confusion.

Rarely, jaundice or abnormal liver function tests occur during alprazolam therapy, with recovery of function after cessation of use.

Episodes of hypomania, mania and other adverse behavioural effects may occur in rare instances with the use of alprazolam, and may necessitate the discontinuation of therapy. Such discontinuation should follow the recommended daily dosage reduction regimen (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Post-Marketing Experience

The following additional adverse effects have been reported:

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
Endocrine disorders	Uncommon	Hyperprolactinaemia

Psychiatric disorders	Uncommon	Hypomania, mania, hallucinations, anger, aggression, hostility, agitation, libido disorder, thinking abnormal, psychomotor hyperactivity
Nervous system disorder	Uncommon	Dystonia
	Not known	Autonomic nervous system imbalance
Gastrointestinal disorders	Uncommon	Gastrointestinal disorder
Hepatobiliary disorders	Uncommon	Hepatitis, hepatic function abnormal, jaundice
Skin and subcutaneous tissue disorders	Uncommon	Dermatitis
	Not known	Angioedema, photosensitivity reaction
Renal urinary disorders	Uncommon	Incontinence, urinary retention
Reproductive system and breast disorders	Uncommon	Sexual dysfunction, menstruation irregular
General disorders and administration site conditions	Not known	Oedema peripheral
Investigations	Uncommon	Intraocular pressure increased

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 an extension of their pharmacologic activity, including respiratory depression and central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms may include drowsiness, mental confusion and lethargy, impaired coordination, diminished reflexes, slurred speech, dilated pupils, absent bowel sounds, and tachycardia. In more serious cases symptoms may include ataxia, hypotonia, hypotension, hypothermia, rhabdomyolysis, atrio-ventricular block, coma and very rarely death. Serious sequelae occur when alprazolam is taken with other drugs and/or ethanol is concomitantly ingested. Deep coma marked hypotension and respiratory depression may indicate other drugs have been ingested as well. In terms of duration, most obtunded patients become arousable within 12 to 36 hours following an acute overdose.

Treatment

In the management of overdosage, it should be borne in mind that multiple agents may have been taken. Treatment of overdosage is primarily supportive of respiratory and cardiovascular function. Following overdosage with KALMA tablets, activated charcoal should be given to reduce absorption. Activated charcoal is most effective when administered within 1-hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected.

The benzodiazepine antagonist flumazenil may be useful in hospitalised patients for the reversal of CNS actions of benzodiazepines. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for re-sedation, respiratory depression, and other residual benzodiazepine effects for an appropriate period after treatment. 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. Please consult the flumazenil product information prior to usage.

Haemoperfusion, forced diuresis and haemodialysis are generally not useful in benzodiazepine intoxication. Ipecac-induced emesis is not recommended due to the potential for CNS depression.

Contact the Poisons Information Centre on 131126 (Australia) for advice on the management of overdosage.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Pharmacological properties of alprazolam in animals appear similar to those of other benzodiazepines, that is, it produces significant anxiolytic, muscle relaxant, sleep promoting and anticonvulsant effects in appropriate animal models.

The exact site and mechanism of action of benzodiazepines is unknown. It is known that they act within the CNS as selective depressants.

Clinical Trials

Clinical studies in healthy volunteers with doses up to 4 mg/day, and in patients with panic disorder at doses up to 10 mg/day, produce only effects which can be considered to be extensions of its pharmacological activities. No clinically significant effects on the cardiovascular or respiratory systems were observed. Alprazolam doses up to 10 mg/day do not clinically affect laboratory parameters or vital signs.

Sleep laboratory studies in humans showed that alprazolam decreased sleep latency, increased duration of sleep and decreased the number of nocturnal awakenings. Alprazolam produced small decreases in both stages 3 to 4 and rapid eye movement (REM) sleep.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration to fasting subjects, alprazolam is rapidly absorbed with almost complete bioavailability. Alprazolam exhibits linear kinetics; after single dose administration of 0.5 to 3 mg, plasma levels of 8 to 40 nanogram/mL were observed; during multiple dose administration of 1.5 to 10 mg/day in divided doses, steady state plasma levels of 18.3 to 100 nanogram/mL were observed. Plasma levels of drug reach steady state within 7 days after starting or altering dosage size. The steady state level is 3 to 4 times that achieved with a single dose.

Peak plasma levels showed a two- to three-fold variation within individual treatment groups. The plasma half-life of alprazolam after single doses in healthy subjects has ranged from 6 to 25 hours. The mean half-life of individual treatment groups ranged from 10 to 14 hours.

Distribution

In vitro alprazolam is bound (80%) to human serum protein. Serum albumin accounts for the majority of the binding.

Metabolism

Alprazolam is extensively metabolised in humans, primarily by cytochrome P450 3A4 (CYP3A4), to two major metabolites in the plasma: 4-hydroxyalprazolam and α-hydroxyalprazolam. A benzophenone derived from alprazolam is also found in humans. Their half-lives appear to be similar to that of alprazolam. The plasma concentrations of 4-hydroxyalprazolam and α-hydroxyalprazolam relative to unchanged alprazolam concentration were always less than 4%. The reported relative potencies in benzodiazepine receptor binding experiments and in animal models of induced seizure inhibition are 0.20 and 0.66, respectively, for 4-hydroxyalprazolam and α-hydroxyalprazolam. Such low concentrations and the lesser potencies of 4-hydroxyalprazolam and α-hydroxyalprazolam suggest that they are unlikely to contribute much to the pharmacological effects of alprazolam. The benzophenone metabolite is essentially inactive.

Excretion

Alprazolam and its metabolites are excreted primarily in the urine. In addition to alprazolam, the major drug-related materials excreted in urine are α-hydroxyalprazolam, and a benzophenone analog. About 50 percent of the dose is excreted within 24 hours, and 94 percent after 72 hours. With chronic dosing, the apparent elimination half-life increases by about 50 percent, possibly because of compartmentalisation effects.

Special Populations

Changes in the absorption, distribution, metabolism and excretion of benzodiazepines have been reported in a variety of disease states including alcoholism, impaired hepatic function and impaired renal function. Changes have also been demonstrated in the elderly. (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.)

Race - Maximal concentrations and half-life of alprazolam are approximately 15% and 25% higher in Asians compared to Caucasians.

Cigarette Smoking - Alprazolam concentrations may be reduced by up to 50% in smokers compared to non-smokers.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Alprazolam was not mutagenic in the in vitro Ames test. Alprazolam did not produce chromosomal aberrations in the in vivo micronucleus assay in rats up to the highest dose tested of 100 mg/kg.

Carcinogenicity

No evidence of carcinogenic potential was observed during 2-year bioassay studies of alprazolam in rats at doses up to 30 mg/kg/day (27 times the maximum recommended daily human dose based on body surface area comparison, assuming a body weight of 50 kg) and in mice at doses up to 10 mg/kg/day (4.5 times the maximum recommended daily human dose based on body surface area comparison, assuming a body weight of 50 kg).

Ocular Effects

When rats were treated orally with alprazolam at 3, 10, and 30 mg/kg/day (2.7 to 27 times the maximum recommended daily human dose based on body surface area comparison, assuming a body weight of 50 kg) for 2 years, a dose related increase in incidence of corneal vascularization was observed in treated males. These lesions did not appear until after more than 11 months of treatment.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

KALMA 0.25, KALMA 0.5, KALMA 1 and KALMA 2 tablets also contain lactose monohydrate, microcrystalline cellulose, maize starch, sodium benzoate, docusate sodium, povidone, colloidal anhydrous silica, sodium starch glycollate and magnesium stearate, erythrosine aluminium lake (KALMA 0.5 only) and indigo carmine aluminium lake (KALMA 0.5 and KALMA 1 only).

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 25°C

6.5 NATURE AND CONTENTS OF CONTAINER

KALMA 0.25: Available in HDPE bottles with a polypropylene (PP) child resistant cap or PVC/PVdC blister pack. – pack sizes of 10 and 50 tablets

KALMA 0.5: Available in HDPE bottles with a polypropylene (PP) child resistant cap or PVC/PVdC blister pack. – pack sizes of 10 and 50 tablets

KALMA 1: Available in HDPE bottles with a polypropylene (PP) child resistant cap or PVC/PVdC blister pack. – pack sizes of 10 and 50 tablets

KALMA 2: Available in HDPE bottles with a polypropylene (PP) child resistant cap or PVC/PVdC blister pack. – pack size of 50 tablets

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 46835 – KALMA 0.25 alprazolam 0.25mg tablet bottle

AUST R 46837 – KALMA 0.5 alprazolam 0.5mg tablet bottle

AUST R 46839 – KALMA 1 alprazolam 1mg tablet bottle

AUST R 63993 – KALMA 2 alprazolam 2mg tablet bottle

AUST R 385850 – KALMA 0.25 alprazolam 0.25mg tablet blister pack

AUST R 385851 – KALMA 0.5 alprazolam 0.5mg tablet blister pack

AUST R 385852 – KALMA 1 alprazolam 1mg tablet blister pack

AUST R 385853 – KALMA 2 alprazolam 2mg tablet blister pack

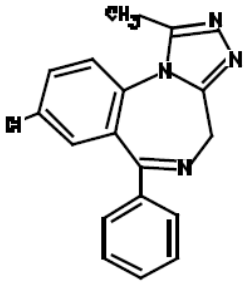
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Chemical name: 8-chloro-1-methyl-6-phenyl-4H-S-triazolo(4,3-α)(1,4)-benzodiazepine



Structural formula:

Molecular formula: $C_{17}H_{13}ClN_4$

Molecular weight: 308.76

Alprazolam is a white crystalline powder which is soluble in methanol or ethanol but has no appreciable solubility in water.

CAS Number

CAS Registry no.: 28981-97-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

S8 (Controlled Drug)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

KALMA 0.25mg, KALMA 0.5mg, KALMA 1mg - 22/10/1993

KALMA 2mg - 18/05/1998

10 DATE OF REVISION

06/11/2024

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
4.3	Update contraindications section
4.4	Update precautions for concomitant use of benzodiazepines and opioids
4.5	Add opioids into medication that produce CNS depression
4.6	Update effects on fertility section
5.3	Update preclinical safety data
8	Update sponsor's details

KALMA® is a Viatris company trade mark

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