

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gerax 250 microgram Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

250 micrograms:

Each tablet contains 250 micrograms alprazolam.

Excipients with known effect:

Each tablet contains 92.77 mg lactose monohydrate.

Each tablet contains 0.10 mg sodium benzoate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

250 micrograms:

White, oval tablets scored and marked "AL 0.25" on one side and "G" on the other.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Anxiety

Benzodiazepines are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration

Posology

Anxiety

Treatment should be as short as possible. The overall duration of treatment generally should not be more than 8 - 12 weeks, including a tapering off process. The patient should be reassessed regularly and the need for continued treatment should be evaluated, especially in case the patient is symptom free.

The recommended starting dose is 500 micrograms to 1 mg daily in divided doses, with increments (no greater than 1 mg every 3 - 4 days), to the level of optimal control usually 3 to 4 mg daily.

To discontinue alprazolam treatment, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of alprazolam be decreased by no more than 0.5 mg every 3 days. Some patients may require an even slower dosage reduction. The risk of dependence may increase with dose and duration of treatment, therefore, the lowest possible effective dose and duration should be used and the need for continued treatment reassessed frequently (see section 4.4).

Elderly

In elderly or debilitated patients, a regimen of 250 micrograms twice daily should be used initially with gradual increments if required and tolerance is assured.

Paediatric population

Safety and efficacy of alprazolam have not been established in children and adolescents below the age of 18 years; therefore use of alprazolam is not recommended.

Method of administration

For oral use.

Treatment should be started with the lower recommended dose. The maximum dose should not be exceeded.

Initial doses may be given at bedtime to minimise daytime lethargy. If side effects occur with the starting dose, the dose should be lowered.

In certain cases extension beyond the maximum treatment period may be necessary, if so, it should not take place without re-evaluation of the patient's status.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1, or to any other benzodiazepine.
- Myasthenia gravis
- Severe respiratory insufficiency
- Sleep apnoea syndrome
- Severe hepatic insufficiency

4.4 Special warnings and precautions for use

Caution is recommended when treating patients with impaired renal function or mild to moderate hepatic insufficiency.

In patients presenting with major depression or anxiety associated with depression, benzodiazepines and benzodiazepine-like agents should not be prescribed alone to treat depression as they may precipitate or increase the risk of suicide. Therefore, alprazolam should be used with caution and the prescription size should be limited in patients with signs and symptoms of a depressive disorder or suicidal tendencies.

Safety and efficacy of alprazolam have not been established in children and adolescents below the age of 18 years, therefore use of alprazolam is not recommended.

Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse (see section 4.5).

A lower dose is also recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression.

Risk from concomitant use of opioids

Concomitant use of Gerax and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as Gerax with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Gerax concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (see section 4.5).

Elderly

Benzodiazepines and related products should be used with caution in elderly, due to the risk of sedation and/or musculoskeletal weakness that can promote falls, often with serious consequences in this population.

It is recommended that the general principle of using the lowest effective dose be followed in older and/or debilitated patients to preclude the development of ataxia or over-sedation.

Dependence

Use of benzodiazepines may lead to the development of physical and psychic dependence upon these products. The risk of dependence increases with dose and duration of treatment, it is also greater in patients with a history of alcohol or drug abuse. Pharmacodependency may occur at therapeutic doses and/or in patients with no individualised risk factor. There is an increased risk of pharmacodependency with the combined use of several benzodiazepines regardless of the anxiolytic or hypnotic indication. Drug abuse is a known risk for alprazolam and other benzodiazepines, and patients should be monitored accordingly when receiving alprazolam. 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. These risks should be considered when prescribing or dispensing alprazolam. To reduce these risks the smallest appropriate quantity should be used and patients should be advised on the proper storage and disposal of unused drug (see section 4.2, 4.8 and 4.9).

Withdrawal symptoms: Once dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion, irritability and insomnia. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures (see section 4.2 and 4.8).

During discontinuation of alprazolam treatment, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of alprazolam be decreased by no more than 0.5 mg every three days. Some patients may require an even slower dosage reduction.

Rebound insomnia and anxiety: a transient syndrome whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, mild dysphoria, anxiety or sleep disturbances, abdominal and muscle cramps, vomiting, sweating, tremor and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually (see section 4.2).

Duration of treatment

It may be useful to inform the patient when treatment is started that it will be of limited duration and to explain precisely how the dosage will be progressively decreased. Moreover it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur while the medicinal product is being discontinued. There are indications that, in the case of benzodiazepines with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high. When benzodiazepines with a long duration of action are being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

Amnesia

Benzodiazepines may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have an uninterrupted sleep of 7-8 hours (see also section 4.8).

Psychiatric and paradoxical reactions

Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines. Should this occur, use of the medicinal product should be discontinued. They are more likely to occur in children and the elderly.

Tolerance

Some loss of efficacy to the hypnotic effects of benzodiazepines may develop after repeated use for a few weeks.

Administration to severely depressed or suicidal patients should be done with appropriate precautions and appropriate size of the prescription.

Episodes of hypomania and mania have been reported in association with the use of alprazolam in patients with depression.

Gerax contains lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Gerax contains sodium benzoate

This medicine contains 0.10 mg sodium benzoate in each tablet.

Gerax contains sodium

This medicine contains less than 1 mmol (23 mg) per tablet, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interactions*Opioids*

The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Gerax with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

Concomitant intake with alcohol is not recommended.

Alprazolam should be used with caution when combined with other CNS depressants.

Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anti-epileptic drugs, anaesthetics and sedative antihistamines. In the case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychological dependence.

CYP3A Inhibitors

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450 3A4) 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 metabolised 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 data available currently, the following recommendations are made:

- The co-administration of alprazolam with ketoconazole, itraconazole, or other azole-type antifungals is not recommended.
- The co-administration of nefazodone or fluvoxamine increases the AUC of alprazolam by approximately 2 fold. Caution and consideration of dose reduction is recommended when alprazolam is co-administered with nefazodone, fluvoxamine, and cimetidine.
- Caution is recommended when alprazolam is co-administered with fluoxetine, propoxyphene, oral contraceptives, diltiazem, or macrolide antibiotics such as erythromycin, clarithromycin and troleandomycin.

CYP3A4 Inducers

Since alprazolam is metabolized by CYP3A4, inducers of this enzyme may enhance the metabolism of alprazolam. Interactions involving HIV protease inhibitors (e.g. ritonavir) and alprazolam are complex and time dependent. Short term, 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.

Digoxin

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

4.6 Fertility, pregnancy and lactationPregnancy

The data concerning teratogenicity and effects on postnatal development and behaviour following benzodiazepine treatment are inconsistent. A large amount of data based on cohort studies indicate that first trimester exposure to benzodiazepine is not

associated with an increase in the risk of major malformation. However, some early case-control epidemiological studies have found a two-fold increased risk of oral clefts.

Benzodiazepines including Gerax should only be used during pregnancy or lactation if considered essential by the physician. Animal studies with benzodiazepines have shown minor effects on the foetus while a few studies have reported late behavioural disturbance in offspring exposed *in utero*.

Benzodiazepine treatment at high dose, during the second and/or the third trimester of pregnancy, has revealed a decrease of foetal active movements and a variability of foetal cardiac rhythm.

When treatment has to be administered for medical reasons during the last part of pregnancy, even at low doses, floppy infant syndrome such as axial hypotonia, sucking troubles leading to a poor weight gain may be observed. These signs are reversible but they may last from 1 up to 3 weeks, according to the half-life of the product. At high doses, respiratory depression or apnoea and hypothermia in newborn may appear. Moreover, neonatal withdrawal symptoms with hyperexcitability, agitation and tremor may be observed a few days after birth, even if no floppy infant syndrome is observed. The apparition of withdrawal symptoms after birth depends on the half-life of the substance.

Alprazolam should not be used during pregnancy unless the clinical condition of the woman requires treatment with alprazolam. If alprazolam is used during pregnancy, or if the patient becomes pregnant while taking alprazolam, the patient should be apprised of the potential hazard to the foetus.

If alprazolam treatment is necessary during last part of pregnancy or during labour, high doses should be avoided and withdrawal symptoms and/or floppy infant syndrome should be monitored in newborn.

Breast-feeding

Alprazolam is excreted in breast milk at low level. However, alprazolam is not recommended during breast-feeding.

4.7 Effects on ability to drive and use machines

Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or to use machines. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased (see section 4.5). These effects are potentiated by alcohol (see section 4.5).

Patients should be cautioned about operating motor vehicles or engaging in other dangerous activities while taking Gerax.

4.8 Undesirable effects

Adverse events, if they occur, are generally observed at the beginning of therapy and usually disappear upon continued medication or decreased dosage.

The following undesirable effects have been observed and reported during treatment with alprazolam with the following frequencies: Very common ($\geq 1/10$); common ($\geq 1/100$ to $<1/10$); uncommon ($\geq 1/1,000$ to $<1/100$); rare ($\geq 1/10,000$ to $<1/1,000$); very rare ($<1/10,000$), not known (cannot be estimated from the available data).

MedDRA System Organ Class	Frequency	Undesirable Effects
Endocrine disorders	Not Known	Hyperprolactinaemia*
Metabolism and nutrition disorders	Common	Decreased appetite
Psychiatric disorders	Very Common	Depression
	Common	Confusional state, disorientation, libido decreased, anxiety, insomnia, nervousness, libido increased*
	Uncommon	Mania* (see section 4.4), hallucination*, anger*, agitation*, drug dependence
	Not Known	Hypomania*, aggression*, hostility*, thinking abnormal*, psychomotor hyperactivity*, drug abuse*
Nervous system disorders	Very common	Sedation, somnolence, ataxia, memory impairment, dysarthria, dizziness, headache
	Common	Balance disorder, coordination abnormal, disturbance in attention, hypersomnia, lethargy,

		tremor
	Uncommon	Amnesia
	Not known	Autonomic nervous system imbalance*, dystonia*
Eye disorders	Common	Vision blurred
	Very Common	Constipation, dry mouth
Gastrointestinal disorders	Common	Nausea
	Not Known	Gastrointestinal disorder*
Hepatobiliary disorders	Not Known	Hepatitis*, hepatic function abnormal*, jaundice*
Skin and subcutaneous tissue disorders	Common	Dermatitis*
	Not known	Angioedema*, photosensitivity reaction*
Musculoskeletal and connective tissue disorders	Uncommon	Muscular weakness
Renal and urinary disorders	Uncommon	Incontinence*
	Not Known	Urinary retention*
Reproductive system and breast disorders	Common	Sexual dysfunction*
	Uncommon	Menstruation irregular*
General disorders and administration site conditions	Very Common	Fatigue, irritability
	Uncommon	Drug withdrawal syndrome*
	Not known	Oedema peripheral*
Investigations	Common	Weight increased, weight decreased
	Not Known	Intraocular pressure increased*

*ADR identified post-marketing

Withdrawal symptoms

Withdrawal symptoms have occurred following rapid decrease or abrupt discontinuance of benzodiazepines including alprazolam. These can range from mild dysphoria and insomnia to a major syndrome, which may include abdominal and muscle cramps, vomiting, sweating, tremor and convulsions. In addition, withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy with alprazolam.

Amnesia

Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour (see section 4.4).

Depression

Pre-existing depression may be unmasked during benzodiazepine use.

Psychiatric and 'paradoxical' reactions

Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepine or benzodiazepine-like agents. They may be quite severe with this product. They are more likely to occur in children and the elderly.

Dependence

Use (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena. Psychic dependence may occur. Abuse of benzodiazepines has been reported (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via HPRC Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

As with other benzodiazepines, overdose should not present a threat to life unless combined with other CNS depressants (including alcohol).

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

Following overdose with oral benzodiazepines, vomiting should be induced (within one hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. The value of dialysis has not been determined. Special attention should be paid to respiratory and cardiovascular functions in intensive care.

Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, slurred speech, mental confusion and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death.

Flumazenil may be used as an adjunct to the management of respiratory and cardiovascular function associated with overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Benzodiazepine derivatives, ATC code: N05BA12

Mechanism of action

Alprazolam, like other benzodiazepines, has a high affinity for the benzodiazepine binding site in the brain. It facilitates the inhibitory neurotransmitter action of gamma-aminobutyric acid which mediates both pre- and post-synaptic inhibition in the central nervous system (CNS).

5.2 Pharmacokinetic properties

Absorption

At least 80% of the oral dose is absorbed.

Distribution

Following oral administration, peak plasma concentrations are reached in about 1.7 hours. After a single oral dose of 500 micrograms, the average maximal concentration was 7.1 ng/ml. There is a linear relationship between the dose and plasma concentration. About 70% of the absorbed dose is bound to plasma proteins.

Biotransformation

Alprazolam is extensively metabolised in the liver, primarily to hydroxylated metabolites, but about 20% of the dose is excreted as unchanged alprazolam.

Elimination

Elimination occurs mostly via the kidneys: 80% of the dose is excreted into the urine and only 7% into the faeces. The mean elimination half-life is 10 - 12 hours.

5.3 Preclinical safety data

Mutagenesis

Alprazolam was not mutagenic in the *invitro* Ames test. Alprazolam did not produce chromosomal aberrations in the *invivo* micronucleus assay in rats up to the highest dose tested of 100 mg/kg, which is 500 times greater than the maximum recommended daily human dose of 10 mg/day.

Carcinogenesis

No evidence of carcinogenic potential was observed during 2-year bioassay studies of alprazolam in rats at doses up to 30 mg/kg/day (150 times the maximum recommended daily human dose of 10 mg/day) and in mice at doses up to 10 mg/kg/day (50 times the maximum recommended daily human dose of 10 mg/day).

Fertility

Alprazolam did not impair fertility in rats up to the highest dose tested of 5 mg/kg/day, which is 25 times the maximum recommended daily human dose of 10 mg/day.

Ocular effects

When rats were treated orally with alprazolam at 3, 10, and 30 mg/kg/day (15 to 150 times the maximum recommended daily human dose of 10 mg/day) for 2 years, a tendency for a dose related increase in the number of cataracts (females) and corneal vascularization (males) was observed. These lesions did not appear until after 11 months of treatment.

Effect of anaesthetic and sedative drugs

Nonclinical research has shown that administration of anaesthetic and sedation drugs that block N-methyl-D-aspartate (NMDA) receptors and/or potentiate gamma-aminobutyric acid (GABA) activity can increase neuronal cell death in the brain and result in long term deficits in cognition and behaviour of juvenile animals when administered during the period of peak brain development. Based on comparisons across nonclinical species, the window of vulnerability of the brain to these effects is believed to correlate with human exposures in the third trimester of pregnancy through the first year of life, but may extend to approximately 3 years of age. While there is limited information of this effect with alprazolam, since the mechanism of action includes potentiation of GABA activity, a similar effect may occur. The relevance of these nonclinical findings to human use is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Cellulose, microcrystalline
Maize starch
Sodium benzoate
Docusate sodium
Povidone
Silica, colloidal anhydrous
Sodium starch glycolate (Type A)
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
2 years (250 microgram blisters only).

6.4 Special precautions for storage

Do not store above 25°C. Keep container in the outer carton.

6.5 Nature and contents of container

Tamper evident polypropylene securitainers fitted with polyethylene white caps and ullage filler. Or alternatively, perforated blister packs of PVC/foil.

Pack size: 100

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Aurobindo Pharma (Malta) Limited
Vault 14, Level 2, Valletta Waterfront
Floriana
FRN 1913
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8 MARKETING AUTHORISATION NUMBER

PA1445/024/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of latest renewal: 08 January 2006

10 DATE OF REVISION OF THE TEXT

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