Professional information

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

MYLAN ALPRAZOLAM 0,25 mg (tablets)

MYLAN ALPRAZOLAM 0,5 mg (tablets)

MYLAN ALPRAZOLAM 1,0 mg (tablets)

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each tablet contains 0,25 mg, 0,5 mg, or 1,0 mg alprazolam.

Excipients with known effect:

Preservative: Sodium benzoate 0,10 mg

Contains sugar: MYLAN ALPRAZOLAM 1,0 mg contains 92,0 mg lactose,

MYLAN ALPRAZOLAM 0.5 mg contains 92,44 mg lactose, MYLAN ALPRAZOLAM 0.25 mg contains 92,76 mg lactose.

For full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

MYLAN-ALPRAZOLAM 0,25 mg tablets are white, ovoid shaped 9 mm by 5,5 mm

MYLAN-ALPRAZOLAM 0,5 mg tablets are pink, ovoid shaped 9 mm by 5,5 mm

MYLAN-ALPRAZOLAM 1,0 mg tablets are lavender, ovoid shaped 9 mm by 5,5 mm

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Mylan Alprazolam is indicated for the treatment of anxiety disorders, or the short-term relief of symptoms of anxiety.
- Anxiety associated with depression is responsive to alprazolam.
- Mylan Alprazolam is also indicated for the treatment of panic disorders for up to eight months.
- The doctor should periodically re-assess the usefulness of Mylan Alprazolam for the individual patient.
- The effectiveness of alprazolam in the treatment of anxiety disorders and anxiety associated with depression, for long-term use exceeding six months has not been established.
- Mylan Alprazolam is only indicated when the anxiety is severe, disabling or subjecting the individual to extreme stress.

4.2 Posology and method of administration

Posology

Treatment should be started with the lowest recommended dose.

A maximum dosage of 4 mg should not be exceeded, except in the treatment of panic disorders.

Treatment should be as short as possible.

The patient should be reassessed regularly and the need for continued treatment should be evaluated, especially in case the patient is symptom free.

The optimum dosage of alprazolam should be individualised based upon the severity of the symptoms and individual patient response.

In 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 medications will require lower doses than those previously treated with minor tranquillisers, antidepressants, or hypnotics or those with a history of chronic alcoholism.

	USUAL STARTING DOSAGE*	USUAL DOSAGE RANGE
Anxiety	0,25 to 0,5 mg given three times daily	0,5 to 4,0 mg daily, given in divided doses
Depression associated with anxiety	0,5 mg given three times daily	1,5 to 4,0 mg daily given in divided doses
Geriatric patients or in the presence of debilitating disease	0,25 mg given two to three times daily	0,5 to 0,75 mg daily, given in divided doses, to be gradually increased if needed and tolerated.
Panic-Related Disorders	0,5 - 1,0 mg given at bedtime	The dose should be adjusted to patient response. Dosage adjustments should be in increments no greater than 1 mg every 3 to 4 days. Additional doses can be added until a three times daily schedule is achieved.

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

Duration of treatment:

The duration of treatment should be as short as possible, but should not exceed eight to twelve weeks in case of anxiety, including tapering off process. Extension beyond these periods should not take place without re-evaluation of the situation. 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 product is being discontinued.

Discontinuation Therapy:

The dosage should be reduced slowly to reduce withdrawal symptoms (*see section 4.4 and 4.8)*. It is suggested that the daily dosage of Mylan Alprazolam be decreased by no more than 0,5 mg every three days. Some patients may require an even slower dosage reduction.

Special Patient Populations

Paediatric patients

The safety and efficacy of Mylan Alprazolam has not been established in children under the age of 18 years *(see section 4.3).*

Elderly patients

Particular caution should be exercised with the elderly and debilitated who are at particular risk of oversedation, respiratory depression and ataxia (the initial oral dosage should be reduced in these patients) (*see section 4.4)*.

Patients with impaired hepatic or renal function

Mylan Alprazolam must be used with caution in patients with impaired renal or hepatic function, pulmonary disease or limited pulmonary reserve (*see section 4.4)*

Method of administration

For oral use.

4.3 Contraindications

- The safety of alprazolam in pregnancy has not been established. Alprazolam should not be administered during pregnancy. Do not administer during labour. Alprazolam given during pregnancy crosses the placenta and may cause the floppy-infant syndrome characterised by central respiratory depression, hypothermia and poor sucking *(see section 4.6*).

- Alprazolam should not be administered to nursing mothers, since alprazolam is excreted in human breast milk *(see section 4.6*).
- Alprazolam is contraindicated in patients with known hypersensitivity to the benzodiazepines or any of the excipients.
- Alprazolam is not recommended for use in patients whose primary diagnosis is psychotic illness e.g. schizophrenia.
- Psychotic patients and patients suffering from mental depression or suicidal tendencies, unless there is a marked component of anxiety in their illness.
- The safety and efficacy of alprazolam has not been established in children under the age of 18 years (*see section 4.2)*. Paradoxical reactions such as excitement and irritability may occur in children. Smaller children are more prone to these reactions.
- Concomitant administration with antiretroviral protease inhibitors, ketoconazole, as the elimination of Mylan Alprazolam is delayed several fold (*see section 4.5*).

4.4 Special warnings and precautions for use

Mylan Alprazolam must be used with caution in patients with impaired renal or hepatic function, pulmonary disease or limited pulmonary reserve.

Mylan-Alprazolam should be used with extreme caution in patients with history of alcohol or drug abuse.

In the case of acute hyperexcitability states, the medicine should be discontinued.

Mylan Alprazolam usage has not been established in certain types of depression *(see section 4.1).*

Mylan Alprazolam produces additive CNS depressant effects when co-administered with alcohol or other medicines producing CNS depression.

The safety and efficacy of Mylan Alprazolam has not been established in children under the age of 18 years *(see section 4.2 and 4.3).*

Mylan Alprazolam should be avoided in psychotic patients and patients suffering from mental depression unless there is a marked component of anxiety in their illness.

Panic disorders have been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients. Therefore, the same precaution must be exercised when using the higher doses of Mylan Alprazolam in treating patients with panic disorders as is exercised with the use of any psychotropic medicines in treating depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans.

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

Care may especially be needed in epileptic patients in whom the initiation or abrupt withdrawal has provoked seizures.

Particular caution should be exercised with the elderly and debilitated who are at particular risk of oversedation, respiratory depression and ataxia (the initial oral dosage should be reduced in these patients) *(see section 4.2)*.

Dependence:

Habituation and emotional/physical dependence may occur with Mylan Alprazolam. Individuals who are prone to abuse medicines, such as alcoholics and drug addicts or patients on other central nervous system (CNS) depressants, should be under careful surveillance while receiving a benzodiazepine e.g. alprazolam because of the predisposition of such patients to habituation and dependence.

Rebound effects/Withdrawal effects:

Once physical 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, vomiting, sweating, tremor, and convulsions. These signs, and symptoms, especially the more serious ones are generally more Frequent in those patients who have received excessive doses over an extended period of time. However, withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken at therapeutic levels.

In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures. A transient syndrome whereby the symptoms that led to treatment with Mylan Alprazolam recur in an enhanced form, may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness.

Since the risk of withdrawal phenomena/rebound is greater after abrupt discontinuation of treatment it is recommended that the dosage is decreased gradually *(see section 4.2 and 4.8).*

Lactose warning:

Mylan Alprazolam contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take Mylan Alprazolam.

Each tablet contains sodium benzoate 0.10 mg.

4.5 Interaction with other medicines and other forms of Interaction

- Alprazolam produces additive central nervous system depressant effects when co-administered with medicines such as barbiturates, alcohol or other central nervous

system depressants. Patients should be cautioned regarding the additive effect of alcohol.

- The steady state plasma concentrations of imipramine and desipramine have been reported to be increased on average of 31 % and 20 % respectively, by the concomitant administration of alprazolam.
- Pharmacokinetic interactions of alprazolam with other medicines have been reported. The clearance of alprazolam can be delayed by the co-administration of cimetidine or macrolide antibiotics.
- Alprazolam did not affect the prothrombin times of plasma warfarin levels in male volunteers who received sodium warfarin orally.
- Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450IIIA4) may increase the concentration of Mylan Alprazolam and enhance its activity.
- Caution and consideration of dose reduction is recommended when Mylan Alprazolam is coadministered with nefazodone and fluvoxamine.
- Caution is recommended when Mylan Alprazolam is co-administered with fluoxetine, oral contraceptives, sertraline, diltiazem, or macrolide antibiotics such as erythromycin and troleandomycin.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of Mylan Alprazolam during pregnancy and lactation has not been established.

Mylan Alprazolam should not be administered during pregnancy (*see section 4.3)*.

The potential for congenital malformations in children of patients who have received Mylan Alprazolam during pregnancy exists.

Mylan Alprazolam should not be administered during labour. Given during labour, it crosses the placenta and may cause the floppy-infant syndrome characterised by central respiratory depression, hypothermia and poor sucking.

Use during lactation

Mylan Alprazolam should not be administered to mothers breastfeeding their infants, since Mylan Alprazolam is excreted in human breast milk (*see section 4.3)*.

Fertility

No information available.

4.7 Effects on ability to drive and use machines

Mylan Aprozolam may have a major influence on mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision. Patients receiving alprazolam as contained in Mylan Alprazolam should be advised not to operate motor vehicles or dangerous machinery, or climb dangerous heights until it is established that they do not become drowsy or dizzy, while receiving alprazolam. In these situations, impaired decision making could lead to accidents.

4.8 Undesirable effects

Side effects are generally observed at the beginning of therapy and usually disappear upon continued medication or decreased dosage.

Summary of the safety profile

- In patients treated for anxiety associated with depression, the most frequent side effects to alprazolam were drowsiness, light-headedness/dizziness and oversedation.

- Drowsiness is more frequent in elderly and debilitated patients and in patients receiving high doses.
- The most frequent adverse reactions in patients with panic-related disorders reported during clinical trials were: sedation/drowsiness/fatigue, ataxia/impaired co-ordination and slurred speech.

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
Metabolism and nutrition disorders	*Frequent*	Decreased appetite
Psychiatric disorders	*Frequent*	Confusional state, depression, irritability, libido decreased
	Less Frequent	Aggression, insomnia, loss of libido, mood disorder, nervousness Hallucinations, agitation, rage
Nervous system disorders	*Frequent*	Sedation**,** somnolence
	Frequent	Ataxia, balance impaired, coordination abnormal, dizziness, headache, memory impairment, dysarthria, hypersomnia, lethargy
	Less Frequent	Amnesia, increased activity, tremor Intellectual impairment, slurred speech
Eye disorders	*Frequent*	Vision blurred
	Less Frequent	Increased intraocular pressure
Gastrointestinal disorders	*Frequent*	Constipation, nausea, dry mouth
	Less Frequent	Diarrhoea, vomiting
Hepatobiliary disorders	*Less Frequent*	Abnormal liver function

Skin and subcutaneous tissue disorders	*Less Frequent*	Dermatitis
Musculoskeletal and connective tissue disorders	*Less Frequent*	Muscle twitching, muscle weakness
Renal and urinary disorders	*Less Frequent*	Enuresis, urinary frequency Urinary retention
Reproductive system and breast disorders	*Less Frequent*	Menstrual irregularities Sexual dysfunction

General disorders and administration site conditions	*Frequent*	Fatigue
Investigations	*Less Frequent*	Jaundice, weight decreased, weight increased

Post-marketing Surveillance:

The following post-marketing events have been reported:

MedDRA System Organ Class	***Frequency***	**Undesirable Effects**
Endocrine disorders	*Less frequent*	Hyperprolactinaemia
Psychiatric disorders	*Less frequent*	Hypomania, mania (*see section 4.4*), hallucination, anger, aggression, hostility, agitation, libido disorder, abnormal thinking, psychomotor hyperactivity
Nervous system disorders	*Less frequent*	Dystonia
	Less frequent	Autonomic nervous system imbalance
Gastrointestinal disorders	*Less frequent*	Gastrointestinal disorder
Hepatobiliary disorders	*Less frequent*	Hepatitis, abnormal hepatic function, jaundice
Skin and subcutaneous tissue disorders	*Less frequent*	Dermatitis
	Less frequent	Angioedema

Renal and urinary disorders	*Less frequent*	Incontinence, urinary retention
Reproductive system and breast disorders	*Less frequent*	Sexual dysfunction, irregular menstruation
General disorders and administration site conditions	*Less frequent*	Peripheral oedema
Investigations	*Less frequent*	Increased intraocular pressure

Description of selected adverse reactions

A transient syndrome whereby the symptoms that led to treatment with Mylan-Alprazolam recur in an enhanced form may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness. Since the risk of withdrawal phenomena/rebound is greater after abrupt discontinuation of treatment it is recommended that the dosage is decreased gradually *(see section 4.2 and 4.4).*

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “Report Drug Reaction Process”, found online under SAHPRA’s safety publications: https://www.sahpra.org.za/

4.9 Overdose

Manifestations of Mylan Alprazolam overdosage include extensions of its pharmacologic activity, namely ataxia and somnolence, confusion, coma, respiratory and cardiovascular depression, hypertension, drowsiness, slurred speech, motor in-coordination. Serious sequela are rare unless other medicines and/or ethanol are concomitantly ingested.

Treatment is systematic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Benzodiazepine derivatives, ATC code: N05BA12

Alprazolam is an anxiolytic agent of the benzodiazepine group.

5.2 Pharmacokinetic properties

Following oral administration, alprazolam is readily absorbed. Peak concentrations in plasma occur in one to two hours following administration. Plasma levels are proportionate to the dose given, over the dose range of 0,5 mg to 3,0 mg, peak levels of 8,0 to 37 ng/ml were observed. The mean half-life of alprazolam is 12-15 hours. Alprazolam and its metabolites are excreted primarily in the urine. The predominant metabolites are hydroxy-alprazolam and a benzophenone derived from alprazolam. In vitro, alprazolam is bound (80 %) to human serum protein.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

• The other ingredients in tablet 0,25 mg**:** Colloidal silica anhydrous, docusate sodium, magnesium stearate, maize starch, microcrystalline cellulose 101, povidone K 30, sodium starch glycollate

• The other ingredients in tablet 0,5 mg**:** Colloidal silica anhydrous, docusate sodium, magnesium stearate, maize starch, microcrystalline cellulose 101, povidone K 30, sodium starch glycollate {colourants: FD&C Blue No 2 CI 73015, Erythrosine Al Lake CI 45430}

• The other ingredients in tablet 1 mg**:** Colloidal silica anhydrous, docusate sodium, magnesium stearate, maize starch, microcrystalline cellulose, povidone K 30, sodium starch glycollate, colourant: FD&C Blue No 2 (Al Lake)}

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30 °C.

Keep container tightly closed.

Protect from light.

6.5 Nature and contents of container

White HDPE bottles of 50 tablets or white polypropylene containers containing 30, 50, 100 or 300 tablets.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Not applicable.

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street,

Isando, Gauteng,

1601

8 REGISTRATION NUMBER(S)

MYLAN-ALPRAZOLAM 0,25 mg tablets : 32/2.6/0372

MYLAN-ALPRAZOLAM 0,5 mg tablets : 32/2.6/0373

MYLAN-ALPRAZOLAM 1,0 mg tablets : 32/2.6/0323

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

February 2000

10 DATE OF REVISION OF TEXT

25 March 2022