SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

ADCO ALZAM 0,25 mg, tablets

ADCO ALZAM 0,5 mg, tablets

ADCO ALZAM 1,0 mg, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **ADCO ALZAM** tablet contains:

0,25 mg, 0,5 mg or 1,0 mg alprazolam

Contains sugar: Lactose hydrous 60,0 mg per tablet

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

ADCO ALZAM 0,25 mg: Round, white, biconvex tablets bisected on one side with "WC" and "787" debossed above and below the bisect respectively.

ADCO ALZAM 0,5 mg: Round, peach, biconvex tablets bisected on one side with "WC" and "786" debossed above and below the bisect respectively.

ADCO ALZAM 1,0 mg: Round, pale blue, biconvex tablets bisected on one side with "WC" and "785" debossed above and below the bisect respectively.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ADCO ALZAM (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 **ADCO ALZAM**. **ADCO ALZAM** is also indicated for the treatment of panic disorders for up to eight months. The doctor should periodically reassess the usefulness of **ADCO ALZAM** (alprazolam) in the treatment of anxiety disorders; anxiety associated with depression, for long-term use exceeding six months has not been established. **ADCO ALZAM** is only indicated when the disorder 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. The maximum recommended dosage should not be exceeded.

The optimum dosage of **ADCO ALZAM** (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.

It is recommended that the general principle of using the lowest effective dose be followed. Patients should be periodically reassessed and dosage adjustments made, as appropriate.

	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
Anxiety associated with depression	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 to 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 or four times daily schedule is achieved. Maximum of 10 mg daily

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

Treatment period

Treatment should be as short as possible. The patient should be reassessed regularly and the need for continued treatment should be evaluated, especially in the case of a patient being symptom free.

The overall duration of treatment should, generally, not be more than 8 to 12 weeks, including a tapering-off process. 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.

Discontinuation therapy

The dosage should be reduced slowly to minimise withdrawal symptoms. It is suggested that the daily dosage of **ADCO ALZAM** be decreased by no more than 0,5 mg every three days. Some patients may require an even slower dosage reduction.

Paediatric population

The safety and efficacy of **ADCO ALZAM** (alprazolam) has not been established in children under the age of 18 years.

Method of administration

For oral administration.

4.3 Contraindications

- Hypersensitivity to benzodiazepines, alprazolam or to any of the excipients listed in section 6.1.
- Pregnancy and breastfeeding (see section 4.6).
- Psychotic patients and patients suffering from mental depression or suicidal tendencies, unless there is a marked component of anxiety in their illness.
- Patients with myasthenia gravis, severe respiratory insufficiency, sleep apnoea syndrome and severe hepatic insufficiency.
- The safety and efficacy of **ADCO ALZAM** has not been established in children under the age of 18 years.
- Concomitant administration with ketoconazole and itraconazole (see section 4.5).

4.4 Special warnings and precautions for use

Dependence

There is a potential for abuse and the development of physical and psychic dependence, especially with prolonged use and high doses. The risk of dependence is also greater in patients with a history of alcohol or drug abuse and patients on other CNS depressants. These patients should therefore be under careful surveillance while receiving a benzodiazepine.

ADCO ALZAM should be used with extreme caution in patients with a history of alcohol or drug abuse.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, mild dysphoria, insomnia, muscle and abdominal pain, extreme anxiety, tension, restlessness, confusion, irritability, vomiting, sweating and tremor.

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.

These signs, and symptoms, especially the more serious ones are generally more common 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 recommended therapeutic levels. Consequently, abrupt discontinuation should be avoided and a gradual tapering in dosage followed. Special care may be needed in epileptic patients in whom the initiation or abrupt withdrawal has provoked seizures.

Rebound effects

A transient syndrome, whereby the symptoms that led to treatment with **ADCO ALZAM** 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 phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.

Risk from concomitant use of opioids

Concomitant use of **ADCO ALZAM** 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 medicines such as **ADCO ALZAM** with opioids should be reserved for patients for whom alternative treatment options are not possible.

If a decision is made to prescribe **ADCO ALZAM** 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 environment to be aware of these symptoms (see section 4.5).

The usual precautions for treating patients with impaired renal or hepatic function, pulmonary disease and limited pulmonary reserve should be observed.

Caution should be exercised in patients suffering from anxiety accompanied by an underlying depressive disorder.

ADCO ALZAM is not recommended for the primary treatment of psychotic illness. **ADCO ALZAM** should not be used alone to treat depression or anxiety with depression; suicide may be precipitated in such patients.

Episodes of hypomania and mania have been reported in association with the use of alprazolam, as in **ADCO ALZAM**, in patients with depression.

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 uninterrupted sleep of 7 – 8 hours (see section 4.8).

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, the use of **ADCO ALZAM** should be discontinued. They are more likely to occur in children and the elderly.

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

Paediatric population

The safety and efficacy of **ADCO ALZAM** (alprazolam) has not been established in children under the age of 18 years. Paradoxical reactions such as excitement and irritability may occur in children. Smaller children are more prone to these reactions.

Duration of treatment

The duration of treatment should be as short as possible (see section 4.2), but should not exceed eight to twelve weeks in case of anxiety, including the 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.

Excipients

ADCO ALZAM contains lactose hydrous. This should be taken into account in patients with diabetes mellitus. Patients with the rare hereditary conditions of galactose intolerance, total lactase

deficiency, or glucose-galactose malabsorption should not take **ADCO ALZAM**.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose making it essentially 'sodium free'.

4.5 Interaction with other medicines and other forms of interaction

ADCO ALZAM (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.

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

The steady state plasma concentrations of imipramine and desipramine have been reported to be increased with the concomitant administration of **ADCO ALZAM** (alprazolam).

Pharmacokinetic interactions of **ADCO ALZAM** with other medications have been reported.

ADCO ALZAM (alprazolam) did not affect the prothrombin times of plasma warfarin levels in male volunteers who received sodium warfarin orally.

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

CYP3A Inhibitors

Compounds that inhibit certain hepatic enzymes (particularly cytochrome P450 3A4) may increase the concentration of **ADCO ALZAM** (alprazolam) and enhance its activity. Data from reported clinical studies with alprazolam, *in-vitro* studies with alprazolam and clinical studies with medicines metabolised similarly to alprazolam provide evidence for varying degrees of interaction and possible interaction with alprazolam for a number of medicines. Based on the degree of interaction and the type of data available, the following recommendations are made:

- The co-administration of **ADCO ALZAM** (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 **ADCO ALZAM** (alprazolam) is co-administered with nefazodone, fluvoxamine and cimetidine.
- Caution is recommended when **ADCO ALZAM** (alprazolam) is co-administered with fluoxetine, propoxyphene, oral contraceptives, sertraline, diltiazem, or macrolide antibiotics such as erythromycin, clarithromycin and troleandomycin.

CYP3A4 Inducers

Since **ADCO ALZAM** (alprazolam) is metabolized by CYP3A4, inducers of this enzyme may enhance the metabolism of **ADCO ALZAM** (alprazolam).

Interactions involving HIV protease inhibitors (e.g. ritonavir) and **ADCO ALZAM** (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 **ADCO ALZAM** (alprazolam).

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of **ADCO ALZAM** (alprazolam) in pregnancy has not been established (see section 4.3).

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

Breastfeeding

ADCO ALZAM (alprazolam) should not be administered to nursing mothers, since alprazolam is excreted in human breast milk (see section 4.3).

4.7 Effects on ability to drive and use machines

Patients receiving **ADCO ALZAM** (alprazolam) should be advised, particularly at the initiation of therapy, 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 **ADCO ALZAM**. 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.

Tabulated summary of adverse reactions

System Organ Class	**Frequency**	**Side effects**
Blood and the lymphatic system disorders	Frequency unknown	Blood disorders
Immune system disorders	Frequency unknown	Hypersensitivity reactions
Endocrine disorders	Frequency unknown	Hyperprolactinaemia

Metabolism and nutrition disorders	Frequent	Decreased appetite
	Less frequent	Change in mass
	Frequency unknown	Anorexia
Psychiatric disorders	Frequent	Disorientation
	Less frequent	Insomnia, nervousness, anxiety, depression, mania, anger, drug dependence
	Frequency unknown	Stimulation, agitation, irritability, concentration difficulties, confusion, hallucinations, other adverse behavioural effects, fatigue, paradoxical excitation, hypomania, aggression, hostility, abnormal thinking, psychomotor hyperactivity, drug abuse
Nervous system disorders	Frequent	Drowsiness, sedation and ataxia, somnolence, dysarthria, dizziness, balance disorder
	Less frequent	Co-ordination disorders, tremor, lethargy, memory impairment, amnesia, headache, autonomic manifestations
	Frequency unknown	Slurred speech
Eye disorders	Less frequent	Blurred vision

	Frequency unknown	Increased intra-ocular pressure
Gastrointestinal disorders	Frequent	Constipation, dry mouth, nausea
	Less frequent	Diarrhoea, Various gastrointestinal symptoms
	Frequency unknown	Changes in salivation
Hepato-biliary disorders	Frequency unknown	Abnormal liver function, jaundice, hepatitis
Skin and subcutaneous tissue disorders	Frequent	Dermatitis
	Frequency unknown	Angioedema, photosensitivity reaction
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Musculoskeletal weakness, dystonia
Renal and urinary disorders	Frequency unknown	Incontinence, urinary retention
Reproductive system and breast disorders	Frequency unknown	Changes in libido, menstrual irregularities, sexual dysfunction
General disorders and administration site conditions	Less frequent	Drug withdrawal syndrome
	Frequency unknown	Peripheral oedema

Description of selected adverse reactions

In patients treated for anxiety, anxiety associated with depression, the most frequent side effects to

ADCO ALZAM (alprazolam) were drowsiness, sedation and ataxia. Drowsiness is more frequent in elderly and debilitated patients and in patients receiving high doses.

In the case of acute, hyperexcitability states, **ADCO ALZAM** (alprazolam) should be discontinued.

Withdrawal symptoms can occur following rapid decrease or abrupt discontinuance of benzodiazepines including **ADCO ALZAM** (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 at 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 benzodiazepines or benzodiazepine-like medicines. They may be quite severe with **ADCO ALZAM** (alprazolam). They are more likely to occur in children and the elderly.

In many of the reported spontaneous case reports of adverse behavioural effects, patients were receiving other CNS medicines 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 of such events. Instances of irritability, hostility and intrusive thoughts have been reported during discontinuance of alprazolam

in patients with post-traumatic stress disorder.

Abuse, dependence and withdrawal

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

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Manifestations of **ADCO ALZAM** (alprazolam) overdosage include extensions of its pharmacological activity, namely ataxia and somnolence, confusion, coma, respiratory and cardiovascular depression and hypotension.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: A 2.6 Tranquillisers

Benzodiazepine derivatives, ATC code: N05BA12

ADCO ALZAM (alprazolam) is an anxiolytic medicine of the benzodiazepine group. Benzodiazepines, including alprazolam, are thought to bind to central nervous system

benzodiazepine receptors, thereby increasing the affinity of the receptor for gamma-aminobutyric acid (GABA). GABA, an inhibitory neurotransmitter, modulates the activity of other neurotransmitter systems, including the noradrenergic system.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, alprazolam is readily absorbed.

Distribution

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.

Biotransformation

The predominant metabolites are α-hydroxy-alprazolam and a benzophenone derived from alprazolam. *In vitro*, alprazolam is bound (70 to 80 %) to human serum protein.

Elimination

The mean half-life of alprazolam is 12 to 15 hours. Alprazolam and its metabolites are excreted primarily in the urine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dioctyl sodium sulfosuccinate (docusate sodium)

Lactose hydrous

Magnesium stearate

Microcrystalline cellulose

Pregelatinised starch

FD & C yellow No.6 Lake (C.I. 15985) (0,5 mg tablet)

FD & C blue No.2 Lake (C.I. 73015) (1,0 mg tablet)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 ºC, in a tightly closed container.

Protect from light.

6.5 Nature and contents of container

30's, 100's and 250's in white polypropylene securitainers or tracer packs or white, round HDPE 90 ml bottle with white polypropylene child resistant closure and heat induction liners in closure.

100's in white polypropylene securitainers or white, round HDPE 90 ml bottle with red polypropylene child resistant closure and heat induction liners in closure.

Not all pack types and pack sizes will be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road,

Erand Gardens,

Midrand, 1685

Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S)

ADCO ALZAM 0,25 mg: 30/2.6/0212

ADCO ALZAM 0,5 mg: 30/2.6/0211

ADCO ALZAM 1,0 mg: 30/2.6/0213

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 May 1996

10. DATE OF REVISION OF THE TEXT

01 August 2023

Namibia:
ADCO ALZAM 0,25 mg: NS3 05/2.6/0258
ADCO ALZAM 0,5 mg: NS3 05/2.6/0259
ADCO ALZAM 1,0 mg: NS3 05/2.6/0260

Botswana:

ADCO ALZAM 0,25 mg: S1C BOT1101787

ADCO ALZAM 0,5 mg: S1C BOT1101788

ADCO ALZAM 1,0 mg: S1C BOT1101789

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