SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

BIOZANE 0,5 mg tablets

BIOZANE 1 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each BIOZANE 0,5 mg tablet contains 0,5 mg alprazolam.

Each BIOZANE 1 mg tablet contains 1,0 mg alprazolam.

BIOZANE contains sugar.

BIOZANE 0,5 mg contains 90,0 mg lactose per tablet.

BIOZANE 1 mg contains 180,0 mg lactose per tablet.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

BIOZANE 0,5 mg tablets are white to almost white, flat, round tablets (diameter 7 mm).

BIOZANE 1 mg tablets are white to almost white, flat, round tablets (diameter 9 mm).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BIOZANE is indicated for the treatment of:

SHORT-TERM RELIEF OF SYMPTOMS OF ANXIETY

TREATMENT OF ANXIETY DISORDERS

Anxiety disorder is a condition corresponding most closely to the latest APA Diagnostic and Statistical Manual [DSM] diagnosis of generalised anxiety disorder.

Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

Diagnostic criteria for Generalised Anxiety Disorder:

A. Generalised, persistent anxiety is manifested by symptoms from three of the following four categories:

1. Motor tension:

Shakiness, jitteriness, jumpiness, trembling, muscle aches, tension, eyelid twitch, inability to relax, furrowed brow, strained face, restlessness and easily startled.

2. Autonomic hyperactivity:

Heart pounding or racing, sweating, cold clammy hands, dry mouth, light-headedness, dizziness, paraesthesias, upset stomach, diarrhoea, discomfort in the pit of the stomach, hot or cold spells, lump in the throat, flushing, pallor, high resting pulse and respiration rate.

3. Apprehensive expectation:

Fear, anxiety, worry, rumination, and anticipation of misfortune to self and others.

4. Vigilance and scanning:

Hyper attentiveness resulting in distractibility, difficulty in concentrating, insomnia, feeling "on edge", impatience and irritability.

B. The anxious mood has been continuous for at least one month.

C. Not due to another mental disorder, such as Depressive Disorder or Schizophrenia.

D. At least 18 years of age.

ANXIETY ASSOCIATED WITH DEPRESSION

MIXED ANXIETY-DEPRESSION

DEPRESSION

Depression can be variously described as neurotic depression, reactive depression, major depressive disorder, etc., depending upon local psychiatric nosology. Usage has not been established in depression with psychiatric features, in bipolar disorders or in "endogenous" depression (i.e., severely depressed inpatients).

PANIC DISORDERS

This includes panic disorder with or without agoraphobia. The essential feature of panic disorder is the unexpected panic attack, a sudden onset of intense apprehension, fear, or terror.

Panic disorder is an illness characterised by recurrent panic attacks. Later in the course of this disturbance, certain issues, 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).

Diagnostic criteria for Panic Disorder:

A. At least three panic attacks within a three-week period in circumstances other than during marked exertion or in a life-threatening situation. The attacks are not precipitated by exposure to a circumscribed phobic stimulus.

B. Panic attacks are manifested by discrete periods of apprehension or fear, and at least four of the following symptoms appear during each attack:

dyspnoea; palpitations; chest pain or discomfort; choking or smothering sensations; dizziness, vertigo, or unsteady feelings; feelings of unreality; paraesthesia (tingling in hands or feet); hot and cold flushes; sweating; faintness; trembling or shaking; smothering sensations, dizziness.

BIOZANE is indicated:

For use of up to six months duration for anxiety and depression and

For up to eight months in the treatment of panic disorder with or without some phobic avoidance.

The effectiveness for long-term use, exceeding six months has not been established.

4.2 Posology and method of administration

Patients should be periodically re-assessed, and dosage adjustments made, as appropriate.

The optimum dose of BIOZANE tablets 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 dose. In general, patients who have not previously received psychotropic medications will require somewhat lower doses than

those previously treated with minor tranquillisers, antidepressants or hypnotics or those with a history of chronic alcoholism.

Posology

	USUAL STARTING DOSE [1)]	**USUAL DOSAGE RANGE**
Anxiety Disorders	0,25 to 0,5 mg given three times daily	0,5 to 4,0 mg daily, given in divided doses.
Mixed anxiety/depression Anxiety associated with depression	0,5 mg given three times daily	1,5 to 4,5 mg daily given in divided doses.
Panic Disorders	0,5 to 1,0 mg given at bedtime or 0,5 mg three times daily	The dose should be adjusted to patient response. Dosage adjustments should be in increments no greater than 1 mg every three to four days. With BIOZANE tablets, additional doses can be added until a three times daily or four times daily schedule is achieved. The mean dose in a large multi-clinic study was 5,7 ± 2,27 mg with occasional patients requiring a maximum of 10 mg daily.
Geriatric patients or in the presence of debilitating disease	0,25 mg given two to three times daily	0,25 to 0,75 mg daily given in divided doses; to be gradually increased if needed and tolerated.

[1)] If side effects occur, the dose should be lowered (see section 4.4)

Initial doses may be given at bedtime to minimise daytime lethargy.

The dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of BIOZANE should be decreased by no more than 0,5 mg every three days. Some patients may require an even slower dosage reduction (see section 4.4).

Special populations

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

In elderly patients, in patients with advanced liver disease or in patients with debilitating disease, the usual starting dose of BIOZANE is given two or three times daily. This may be gradually increased if needed and tolerated. The elderly may be especially sensitive to the effects of benzodiazepines. If side effects occur at the recommended starting dose, the dose may be lowered.

Paediatric population

The safety and efficacy of BIOZANE has not been established in children under the age of 18 years.

Method of administration

Oral administration

4.3 Contraindications

BIOZANE is contraindicated in patients with known hypersensitivity to the active substance (alprazolam), benzodiazepines, or to any excipient (see section 6.1).

BIOZANE is not recommended for use in patients whose primary diagnosis is schizophrenia.

Concomitant administration with antiretroviral protease inhibitors, ketoconazole, itraconazole or other azole-type antifungals as the elimination of BIOZANE is delayed several folds (see section 4.5).

The safety and efficacy of BIOZANE has not been established in children below the age of 18 years.

BIOZANE is also contraindicated in patients with myasthenia gravis, severe respiratory insufficiency, sleep apnoea syndrome and severe hepatic insufficiency.

4.4 Special warnings and precautions for use

Depression/anxiety

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

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

In patients presenting with major depression or anxiety associated with depression benzodiazepines and benzodiazepine-like medicine should not be prescribed alone to treat depression as they may precipitate or increase the risk of suicide. Therefore BIOZANE 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.

Renal and hepatic impairment

Caution is recommended when treating patients with impaired renal function or mild to moderate hepatic insufficiency (see section 4.3).

There have been rare reports of death in patients with severe pulmonary disease shortly after the initiation of treatment with BIOZANE 0,25.

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. 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 and insomnia.

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 (see section 4.2).

Abrupt discontinuation of BIOZANE must be avoided as withdrawal symptoms have occurred following rapid decrease or abrupt discontinuation. Dosage must be gradually tapered to preclude sequel of rapid withdrawal (see section 4.2 for dose reduction during withdrawal period).

Symptoms can range from mild dysphoria and insomnia to a major syndrome which may include abdominal and muscle cramps, vomiting, sweating, tremor and occasionally convulsions. 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.

However, withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken at therapeutic levels. Consequently, abrupt discontinuation should be avoided and a gradual tapering in dosage followed. Care my especially be needed in epileptic patients in whom the initiation or abrupt withdrawal has provoked seizures.

A transient syndrome whereby the symptoms that led to treatment with BIOZANE 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 (see section 4.2).

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 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 decrease. 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 product is being discontinued.

The usual precautions for treating patients with impaired renal or hepatic function, pulmonary disease and limited

pulmonary reserve should be observed.

BIOZANE should be used with extreme caution in patients with history of alcohol or drug abuse.

Elderly and debilitated patients

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

Risk from concomitant use of opioids

Concomitant use of BIOZANE 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 BIOZANE with opioids should be reserved for patients whom alternative treatment options are not possible.

If a decision is made to prescribe BIOZANE concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see 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 the patients and their environment to be aware of these symptoms (see section 4.5)

Amnesia

Benzodiazepines may induce anterograde amnesia. The condition occurs most often several hours after ingesting the medication 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).

Psychiatric and paradoxical reactions

Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other behavioural adverse behavioural effects are known to occur when

using benzodiazepines. Should this occur, use of the medication should be discontinued. They are more likely to occur in children and elderly.

Tolerance

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

BIOZANE contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take BIOZANE.

The safety and efficacy of BIOZANE 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.

4.5 Interaction with other medicines and other forms of interaction

Opioids

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

BIOZANE produces additive central nervous system depressant effects when co-administered with medicines such as barbiturates, alcohol or other central nervous system depressants. Patients must 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 BIOZANE.

CYP3A Inhibitors

Pharmacokinetic interactions can occur when BIOZANE is administered along with medicines that interfere with its metabolism. Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450 3A4) may increase the concentration of BIOZANE and enhance its activity. Data from clinical studies with medicines metabolised similarly to BIOZANE provide evidence for varying degrees of interaction and possible interaction with BIOZANE for a number of medicine. Based on the degree of interaction and the type of data available, the following recommendations are made:

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

Caution is recommended when BIOZANE is co-administered with fluoxetine, oral contraceptives, sertraline, diltiazem, or macrolide antibiotics such as erythromycin, clarithromycin and troleandomycin.

BIOZANE did not affect the prothrombin times of plasma warfarin levels in male volunteers who received sodium warfarin orally.

CYP3A4 Inducers

Since BIOZANE 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 BIOZANE (see section 4.3).

Digoxin

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of BIOZANE during pregnancy has not been established. The potential for congenital malformations in children of patients who have received BIOZANE during pregnancy exists. BIOZANE 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.

Breastfeeding

BIOZANE should not be administered to mothers breastfeeding their infants, since BIOZANE is excreted in human breast milk

4.7 Effects on ability to drive and use machines

Patients receiving BIOZANE should be advised not to operate motor vehicles or dangerous machinery or climb dangerous heights until it is established that they do not became drowsy or dizzy while receiving BIOZANE. In these situations, impaired decision making could lead to accidents.

4.8 Undesirable effects

MedDRA System Organ Class	***Frequency***	**Undesirable Effects**
Metabolism and nutrition disorders	*Frequent*	Decreased appetite
Psychiatric disorders	*Frequent*	Confusional state, depression, irritability, libido decreased, disorientation, anxiety
	Less frequent	Aggression, insomnia, loss of libido, mood disorder, nervousness, hallucinations, agitation, rage
Nervous system disorders	*Frequent*	Sedation, somnolence, ataxia, balance impaired, coordination abnormal, dizziness, headache, memory

		impairment, dysarthria, hypersomnia, lethargy
	Less Frequent	Amnesia, increased activity, tremor, intellectual impairment, slurred speech, concentration difficulties
Eye Disorders	*Frequent*	Vision blurred
	Less frequent	Increased intraocular pressure
Gastrointestinal disorders	*Frequent*	Constipation, nausea, dry mouth
	Less frequent	Diarrhoea, vomiting, change in mass
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, irritability
Blood disorders	*Frequency unknown*	Blood disorder
Investigations	*Less frequent*	Jaundice, weight decreased, weight increased

Post-marketing Surveillance:

The following most-marketing events have been reported with BIOZANE:

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, 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, 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

Withdrawal symptoms have occurred following rapid decrease or abrupt discontinuance of benzodiazepines including BIOZANE. 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 BIOZANE.

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 BIOZANE 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 medicine. They may be quite severe with BIOZANE. They are more likely to occur in children and the elderly.

In many of the spontaneous case reports of adverse behavioural effects, patients were receiving other CNS medicine 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.

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 (see section 4.4). Psychic dependence may occur. Abuse of benzodiazepines has been reported.

Reporting of suspected adverse reaction

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 BIOZANE overdosage include extensions of its pharmacological activity, namely ataxia and somnolence, confusion, coma, respiratory and cardiovascular depression and hypotension. Serious sequela are rare unless other medicines and/or ethanol are concomitantly ingested. Treatment of overdosage is primarily supportive of respiratory and cardiovascular function. The value of dialysis has not been determined. 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

Pharmacological classification: A.2.6 Tranquilisers

ATC code: NO5BA12

Pharmacotherapeutic group: Alprazolam is an anxiolytic agent 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 almost completely bioavailable.

Steady-state plasma concentrations are achieved within three to four days of continuous dosing. 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 mg/mL were observed. The mean half-life of alprazolam is 12-15 hours.

Distribution

In vitro, alprazolam is bound (80 %) to human serum protein.

Biotransformation

The predominant metabolites are alpha- hydroxy-alprazolam and a benzophenone derived from alprazolam. Although they possess some pharmacological activity, the plasma levels of these metabolites are extremely low during chronic dosing.

Elimination

Alprazolam and its metabolites are excreted primarily in the urine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose

Maize Starch

Gelatin

Magnesium Stearate

6.2 Incompatibilities

None

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25˚ C.

Protect from moisture and light.

6.5 Nature and contents of container

Glass container

Brown, amber glass container closed with a pilfer-proof closure lined with expanded polyethene, aluminium and polyester film.

Pack size: 30 or 100 tablets.

Blister pack

Transparent PVC/PVDC and silver Alu blister strips; 10 tablets per blisters strip.

Pack size: 30 or 100 tablets.

HPDE container

A 60 cc or 100cc white, opaque HDPE container with white Opaque Polypropylene Fine ribbed 33mm screw cap with induction sealing wad.

Pack size: 30 or 100 tablets.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground Floor, Bock K,

400, 16th Road, Halfway House

Randjiespark

1685

8. REGISTRATION NUMBERS

BIOZANE 0,5 mg: 28/2.6/0001

BIOZANE 1 mg: 28/2.6/0002

9. DATE OF FIRST AUTHORISATION

10 December 1993

10. DATE OF REVISION OF THE TEXT

30 April 2024