National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) BIOZEP INJECTION

1. NAME OF THE MEDICINAL PRODUCT

(Biozep Injection) Diazepam Injection BP 10mg/2ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Diazepam BP	10 mg
Benzyl Alcohol BP	1.5%v/v
Propylene Glycol BP	Q.S

Batch size 100.0 liter

S/N	INGREDIENTS	GRADE	TYPE	QUANTITY FOR 100.0 LITRE	QUANTITY FOR 1 ML
1	Diazepam	BP	A	0.5525 kg	5.25 mg
2	Propylene glycol	BP	E	72.0 L	0.72 ml
3	Benzyl alcohol	BP	P	1.5 L	0.015 ml
4	Sodium benzoate	BP	E	0.205kg	2.05mg
5	Benzoic acid	BP	E	0.045kg	0.45mg
6	Sodium hydroxide	BP	E	0.0041kg	0.041mg
7	Water for injection	BP	-	Q.S to make 100.0 L	q.s to 1ml

3. PHARMACEUTICAL FORM

A clear colourless solution filled in amber coloured sealed glass ampoule with blue dot at constriction.

4. Clinical particulars

4.1 Therapeutic indications

Diazepam is an anxiolytic, anticonvulsant and central muscle-relaxant. Diazepam is used to relieve anxiety and provide sedation in severe acute anxiety or agitation and for the management of agitation associated with delirium tremens.

Diazepam is used to relieve acute muscle spasm and tetanus.

Acute convulsions including status epilepticus, also convulsions due to poisoning and febrile convulsions

As an adjunct during endoscopy, in dentistry, surgery, radiology

Cardiac catheterisation, cardioversion, used pre-operatively to relieve anxiety, provide sedation, light anaesthesia and anterograde amnesia

4.2 Posology and method ofadministration

Diazepam Injection BP may be given IV, IM or by IV infusion.

Adults:
Severe acute anxiety or agitation:
10 mg IV or IM injection which may be repeated after an interval of not less than 4 hours

Delirium Tremens:
10 – 20 mg IV or IM
Higher doses may be needed depending on severity of symptoms.

Acute Muscle Spasm:
10 mg IV or IM injection which may be repeated after an interval of not less than 4 hours

Tetanus:
Initially an IV dose of 0.1 - 0.3 mg/kg body weight, repeated at intervals of 1 - 4 hours.
Continuous IV infusion of 3 – 10 mg/kg body weight per 24 hours can also be used. The chosen dose should be related to the severity of the case and in extremely severe cases higher doses have been used.

Status epilepticus, convulsions due to poisoning:
10 – 20 mg IV or IM, repeated if necessary 30 - 60 minutes later.
If indicated, this may be followed by slow intravenous infusion (maximum dose 3 mg/kg body weight over 24 hours).

Pre-operative medication or premedication:
0.2 mg/kg body weight, the usual adult dose is 10 – 20 mg but higher doses may be necessary according to the clinical response.

Elderly or Debilitated Patients:
Doses should not exceed half those normally recommended

Children:
Status epilepticus, convulsions due to poisoning, febrile convulsions:
0.2 - 0.3 mg/kg body weight IV (or IM) or 1 mg per year of life

Tetanus:
As for adults
Pre-operative medication or premedication:
0.2 mg/kg body weight, the injection should be given slowly (0.5 ml per minute).

Neonates:
Not recommended; dosage has not been established.

IMPORTANT: In order to reduce the likelihood of adverse effects during intravenous administration the injection should be given slowly (1.0ml solution per minute). It is advisable to keep the patient supine for at least an hour after administration. Except in emergencies, a second person should always be present during intravenous use and facilities for resuscitation should always be available.

It is recommended that patients should remain under medical supervision until at least one hour has elapsed from the time of injection. They should always be accompanied home by a responsible adult, with a warning not to drive or operate machinery for 24 hours.

Intravenous injection may be associated with local reactions and thrombophlebitis and venous thrombosis may occur. In order to minimise the likelihood of these effects, intravenous injections of diazepam should be given into a large vein of the antecubital fossa.

4.3 Contraindications

- Known hypersensitivity to diazepam, other benzodiazepines, propylene glycol or any of the other product excipients.
- Phobic or obsessional states; chronic psychosis, hyperkinesis (paradoxical reactions may occur)
- Acute pulmonary insufficiency, respiratory depression, acute or chronic severe respiratory insufficiency (ventilator failure may be exacerbated)
- Sleep apnoea condition may be exacerbated).
- Marked neuromuscular respiratory weakness including unstable myasthenia gravis (condition may be exacerbated).
- Severe hepatic impairment (elimination half-life of diazepam may be prolonged).
- Acute porphyria
- Planning a pregnancy
- Pregnancy

Diazepam Injection should not be used alone in the treatment of depression or anxiety associated with depression due to the risk of precipitation of suicide in this patient group.

4.4 Special warnings and precautions for use

The IM use of diazepam injection can lead to a rise in serum creatinine phosphokinase activity, with a maximum level occurring between 12 and 24 hours after injection. This fact should be taken into account in the differential diagnosis of myocardial infarction.

The absorption from IM injection of diazepam may be variable, particularly for the gluteal muscles. This route of administration should only be used if IV administration is not possible.

Diazepam Injection BP contains propylene glycol. There have been rare reports of propylene glycol toxicity (e.g. increased anion gap, metabolic acidosis, hyperosmolality, renal impairment) with the potential for organ system failure and circulatory shock, in patients treated with continuous infusions of diazepam. Central nervous system toxicity, including seizures, as well as unresponsiveness, tachypnoea, tachycardia and diaphoresis have also been associated with propylene glycol toxicity. Symptoms may be more likely to develop in patients with renal or hepatic impairment and in paediatric patients.

Concomitant use of alcohol/CNS depressants

The concomitant use of diazepam with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of diazepam possibly including severe sedation, clinically relevant respiratory and/or cardio-vascular depression

Tolerance

Loss of efficacy effects may develop after repeated use for a few weeks. Limits of tolerance in patients with organic cerebral changes (particularly arteriosclerosis) or cardiorespiratory insufficiency may be very wide care must be taken in adapting the dosage with such patients.

Dependence

The risk of dependence (physical or psychological) increases with dose and duration of treatment and is greater in patients with a history of alcohol or drug abuse, or in patients with a marked personality disorder. Therefore;

- Regular monitoring of such patients is essential
- Routine repeat use should be avoided
- Treatment should be withdrawn gradually
- Abuse of diazepam has been reported.

Withdrawal effects

The duration of treatment should be as short as possible.

If physical dependence has developed, abrupt termination of treatment results in withdrawal symptoms. These include headache, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability; sleep disturbance, diarrhoea and mood changes. In severe cases the following may occur: a feeling of unreality or of being separated from the body, derealisation, depersonalisation, confusional states, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, psychotic manifestations including hallucinations or epileptic seizures. Withdrawal symptoms will be worse in patients who have been dependent on alcohol or other narcotic drugs in the past, but can occur following abrupt cessation of treatment in patients receiving normal therapeutic doses for a short period of time.

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, anxiety or sleep disturbances 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.

4.5 Interaction with other medicinal products and other forms of interaction

Particular attention should be paid to the potential effects of drug interactions with diazepam in the elderly.

Not recommended

Alcohol

Diazepam should not be used together with alcohol (CNS inhibition enhanced sedative effects: impaired ability

to drive/ operate machinery).

Sodium oxybate
Avoid concomitant use (enhanced effects of sodium oxybate)

HIV-protease inhibitors
Avoid concomitant use (increased risk of prolonged sedation)

Take into account
Pharmacodynamic interactions
If diazepam is used with other centrally acting agents, careful consideration has to be given to the pharmacology of the agents employed, particularly with compounds that may potentiate or be potentiated by the action of diazepam, such as neuroleptics, anxiolytics/sedatives, hypnotics, antidepressants, anticonvulsants, sedating antihistamines, antipsychotics, anaesthetics for general anaesthesia and narcotic analgesics. Such concomitant use may increase sedative effects and cause depression of respiratory and cardiovascular functions. Concomitant use of narcotic analgesics may promote psychological dependency due to enhancement of euphorigenic effects.

Anti-epileptic drugs
Pharmacokinetic studies on potential interactions between diazepam and antiepileptic drugs have produced conflicting results. Depression and elevation of drug levels, as well as no change, have been reported.
Phenobarbital taken concomitantly may result in an additive CNS effect; increased risk of sedation and respiratory depression. Phenobarbital is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam; it reduces the effect of diazepam.

Special care should be taken in adjusting the dose in the initial stages of treatment.
Side effects may be more evident with hydantoins or barbiturates.
Diazepam has been reported to be displaced from protein-binding sites by sodium valproate (increased serum levels: increased risk of drowsiness).

Narcotic analgesics
Enhancement of the euphoria may lead to increased psychological dependence.

Other drugs enhancing the sedative effect of diazepam

- Cisapride, lofexidine, nabilone, disulfiram and the muscle-relaxants – baclofen, Tizanidine, suxamethonium and tubocurarine
- Compounds that affect hepatic enzymes (particularly cytochrome P450):
  Inhibitors (eg cimetidine: isoniazid: erythromycin: omeprazole: esomeprazole) reduce clearance and may potentiate the action of benzodiazepines.
  Itraconazole, ketoconazole, and to a lesser extent fluconazole and voriconazole are potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma levels of benzodiazepines. The effects of benzodiazepines may be increased and prolonged by concomitant use. A dose reduction of the benzodiazepine may be required.

Rifamycins (rifampicin)

Rifampicin is a potent inducer of CYP3A4 and substantially increases the hepatic metabolism and clearance of diazepam. In a study with healthy subjects administered 600 mg or 1.2 g rifampicin daily for 7 days, the clearance of diazepam was increased by about fourfold. Co-administration with rifampicin gives rise to substantially decreased concentrations of diazepam; reduced effect of diazepam. The concomitant use of rifampicin and diazepam should be avoided.

Antihypertensives, vasodilators & diuretics

There is enhanced hypotensive effect with ACE inhibitors, alpha-blockers, angiotensin–II receptor antagonists, calcium channel blockers adrenergic neurone blockers, betablockers, moxonidine, nitrates, hydralazine, minoxidil, sodium nitroprusside and diuretics.

Enhanced sedative effect with alpha-blockers or moxonidine

Dopaminergics

Possible antagonism of the effect of levodopa

Antiviral agents (atazanavir, ritonavir, delavirdine, efavirenz, indinavir, nelfinavir, saquinavir)

Antiviral agents may inhibit the CYP3A4 metabolic pathway for diazepam. There is increased risk of sedation and respiratory depression. Therefore, concomitant use should be avoided.

4.6 Pregnancy and Lactation

Pregnancy

There is no evidence regarding the safety of diazepam in human pregnancy, nor is there evidence from animal studies, that it is free from hazard. Do not use during pregnancy, especially during the first and last trimesters unless there are compelling reasons.

If diazepam is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of diazepam if she intends to become, or suspects that she is pregnant.

Results of retrospective studies suggest an increased risk of congenital malformation in infants or mothers who received diazepam during the first trimester of pregnancy.

Infants born to mothers who take benzodiazepines chronically during the later stages of pregnancy may develop physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period.

An increase in foetal heart rate has occurred after diazepam use during labour.

Hypoactivity, hypotonia, hypothermia, apnoea, feeding problems, hyperbilirubinaemia and kernicterus have been reported in neonates born to mothers who receive large doses of diazepam (generally greater than 30 mg) shortly before delivery.

Breast-feeding

Diazepam has been detected in breast milk. If possible diazepam should be avoidedduring breast feeding.

Fertility

Studies in animals have shown a decrease in pregnancy rate and reduced number of surviving offspring in rats at high doses. There are no human data.

4.7 Effects on ability to drive and use machines

Sedation, amnesia and impaired muscular function may adversely affect the ability to drive or use machines. If insufficient sleep occurs, the likelihood of impaired alertness may be increased. Patients should be warned that effects on the central nervous system may persist into the day after administration even after a single dose.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. When prescribing this medicine the patient should be told:

- The medicine is likely to affect ability to drive
- Do not drive until you know how the medicine affects you

4.8 Undesirable effects

Drowsiness, numbed emotions, reduced alertness, confusion, fatigue, headache, dizziness, muscle weakness, ataxia or double vision predominantly occur at the start of therapy but usually disappear with repeated administration. Among elderly patients there may be confusion conditions at high dose levels. There is an increased risk of falls and associated fractures in elderly patients using benzodiazepines.

Increased salivary and bronchial secretion has been reported, in particular in children.

Amnesia

Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour.

Dependence

Chronic use (even at therapeutic doses) may lead to the development of physical and psychological dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena. Abuse of benzodiazepines has been reported.

The frequencies of adverse events are ranked according to the following:
Very Common (≥1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000)

System Organ Class	Frequency	Undesirable effects
Blood and lymphatic system disorders	Rare	Blood dyscrasias
	Very Rare	Leukopenia, Thrombocytopenia, Agranulocytosis
Immune system disorders	Very Rare	Hypersensitivity reactions, including anaphylaxis
Psychiatric disorders	Common	Confusion

	Rare	Psychiatric and paradoxical reactions such as excitation, restlessness, agitation, irritability, aggressiveness, delusion, rages, hallucinations, psychoses, memory loss, nightmares, inappropriate behaviour and other adverse, behavioural effects
Nervous system disorders	Very common	Drowsiness
	Common	Ataxia, impaired motor ability, tremor
	Uncommon	Anterograde amnesia, Concentration difficulties, balance disorders, dizziness, headache, slurred speech
	Rare	Unconsciousness, insomnia, dysarthria
Eye disorders	Not known	Reversible disorders of vision: blurred vision, diplopia, nystagmus
Ear and Labyrinth disorders	Not known	Vertigo

These reactions are known to occur when using benzodiazepines or benzodiazepine-like agents. These reactions may be quite severe. They are more likely to occur in children and the elderly. Diazepam should be discontinued if such symptoms occur.

Pre-existing depression may be unmasked during benzodiazepine use.
This may occur when using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour.

The likelihood and degree of severity of withdrawal symptoms is dependent on the duration of treatment, dose level and degree of dependency. In severe cases the following symptoms may occur: derealisation, depersonalisation, tinnitus, numbness and tingling of the extremities, hypersensitivity to light, noise, and physical contact, involuntary movements, hyperreflexia, tremor, nausea, vomiting, diarrhoea, abdominal cramps, loss of appetite, agitation, palpitations, tachycardia, panic attacks, vertigo, short-term memory loss, hallucinations/delirium, catatonia, hyperthermia, convulsions. Convulsions may be more common in patients with pre-existing seizure disorders, or those taking other drugs that lower the convulsive threshold such as antidepressants.

4.9 Overdose

Features

The symptoms of diazepam overdose are mainly an intensification of the therapeutic effects (ataxia, drowsiness, dysarthria, sedation, muscle weakness, profound sleep, hypotension, bradycardia, nystagmus) or paradoxical excitation. In most cases only observation of vital functions is required.

Extreme overdosage may lead to coma, areflexia, cardiorespiratory depression and apnoea, requiring appropriate countermeasures (ventilation, cardiovascular support).

Benzodiazepine respiratory depressant effects are more serious in patients with severe chronic obstructive airways disease. Severe effects in overdose also include rhabdomyolysis and hypothermia.

Rarely, propylene glycol toxicity has been reported following higher than recommended doses.

Management

Maintain a clear airway and adequate ventilation.

Monitor level of consciousness, respiratory rate, pulse oximetry and blood pressure in symptomatic patients.

Consider arterial blood gas analysis in patients who have a reduced level of consciousness (GCS < 8; AVPU scale P or U) or have reduced oxygen saturations on pulse oximetry.

Correct hypotension by raising the foot of the bed and by giving an appropriate fluid challenge. Where hypotension is thought mainly due to decreased systemic vascular resistance, drugs with alpha-adrenergic activity such as noradrenaline or high dose dopamine (10-30 micrograms/kg/min) may be beneficial. The dose of inotrope should be titrated against blood pressure.

If severe hypotension persists despite the above measures, then central venous pressure monitoring should be considered.

Supportive measures are indicated depending on the patient's clinical state.

Benzodiazepines are poorly dialysable.

Flumazenil, a benzodiazepine antagonist, is not advised as a routine diagnostic test in patients with reduced conscious level. It may sometimes be used as an alternative to ventilation in children who are naive to benzodiazepines, or in patients with COPD to avoid the need for ventilation. It is not necessary or appropriate in cases of poisoning to fully reverse the benzodiazepine effect. Flumazenil has a short half-life (about an hour) and in this situation an infusion may therefore be required. Flumazenil is contraindicated when patients have ingested multiple medicines, especially after co-ingestion of a benzodiazepine and a tricyclic antidepressant or any other drug that causes seizures. This is because the benzodiazepine may suppress seizures induced by the second drug; its antagonism by flumazenil can reveal severe status epilepticus that is very difficult to control.

The use of flumazenil is not recommended in epileptic patients who have been receiving benzodiazepine treatment for a prolonged period. Although flumazenil exerts a slight intrinsic anticonvulsant effect, the abrupt suppression of the protective effect of a benzodiazepine agonist can give rise to convulsions in epileptic patients.

Contraindications to the use of flumazenil include features suggestive of a tricyclic antidepressant ingestion including a wide QRS, or large pupils. Use in patient’s postcardiac arrest is also contraindicated. It should be used with caution in patients with a history of seizures, head injury, or chronic benzodiazepine use.

Occasionally a respirator may be required but generally few problems are encountered, although behavioural changes are likely in children.

If excitation occurs, barbiturates should not be used.

Effects of overdose are more severe when taken with centrally-acting drugs, especially alcohol, and in the absence of supportive measures, may prove fatal.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic Group: Benzodiazepines

ATC Code: N05BA01

Diazepam is a benzodiazepine tranquilliser with anticonvulsant, sedative, muscle relaxant and amnesic properties. It is used in the treatment of anxiety and tension states, as a sedative and pre-mendicant, in the control of muscle spasm as in tetanus, and in the management of alcohol withdrawal symptoms. It is of value in patients undergoing orthopaedic procedures endoscopy and cardioversion.

5.2 Pharmacokinetic properties

Diazepam is metabolised to two active metabolites, one of which, desmethyldiazepam, has an extended half-life. Diazepam is therefore a long acting benzodiazepine and repeated doses may lead to accumulation.

Diazepam is metabolised in the liver and excreted via the kidney. Impaired hepatic or renal function may prolong the duration of action of diazepam. It is recommended that elderly and debilitated patients receive initially one half the normal recommended dose.

During prolonged administration, for example in the treatment of tetanus, the dosage should generally be reduced after 6-7 days, to reduce the likelihood of accumulation and prolonged CNS depression.

5.3 Preclinical safety data

Chronic toxicity studies have demonstrated no evidence of drug induced changes. There are no long-term animal studies to investigate the carcinogenic potential of diazepam.

Several investigations pointed to a weakly mutagenic potential at doses far above the human therapeutic dose.

Local tolerability has been studied following single and repeat dose applications into the conjunctival sac of rabbits and the rectum of dogs. Only minimal irritation was observed. There were no systemic changes.

In humans it would appear that the risk of congenital abnormalities from the ingestion of therapeutic doses of benzodiazepines is slight, although a few epidemiological studies have pointed to an increased risk of cleft palate. There are case reports of congenital abnormalities and mental retardation in prenatally exposed children following over dosage and intoxication with benzodiazepines.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol BP

Propylene glycol BP

Sodium benzoate B

Benzoic acid BP

Sodium Hydroxide BP

Water for Injection BP

6.2 Incompatibilities

Diazepam injection should not be mixed with other drugs or IV fluids and should not normally be diluted except when given slowly in large intravenous infusions of normal saline or dextrose. Not more than 40 mg of diazepam should be added to 500 ml infusion solution. The solution should be freshly made up and used within six hours.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C, keep container in outer carton in order to protect from light

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

10 x 2ml amber coloured glass Ampoules in a carton along with a pack insert

6.6 Special precautions for disposal <and other handling>

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT

Biopharma Nigeria Limited

10, Odogunyan Palace Road,

Shagamu Road,

Ilorodu,

Lagos state,

Nigeria

MANUFACTURER

Alpa Laboratories Limited

33/2 A.B Road, Pigdamber, Indore (MP),

India.

Pin Code- 453446

+91 731 4294567

+91 731 4294444