1.17 SUMMARY OF PRODUCT CHARACTERISTICS

1.17.1 Product Information for Health Professionals

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

VERZEPAM (Diazepam Injection BP, 5mg/ml)

2. Qualitative and Quantitative composition

Qualitative composition

Each ml contains

Diazepam BP

Benzyl Alcohol BP

(As preservative)

Water for Injection BP

Quantitative composition

Each ml contains	
Diazepam.BP	5 mg
Benzyl Alcohol BP	2% v/v
(As preservative)	
Water for Injection BP	q.s.

3. Pharmaceutical form

Sterile clear colorless to light yellow solution for injection by IV and IM route.

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 of administration

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).Diazepam injection should be given into a large vein of the antecubital fossa, the patient in a supine position throughout the procedure to reduce the possibility of hypotension or apnoea occurring.

4.3 Contraindications

- Known hypersensitivity to diazepam, other benzodiazepines or propylene glycol.
- Acute pulmonary insufficiency or respiratory depression.
- Sleep apnoea syndrome.
- Marked neuromuscular respiratory weakness including unstable myasthenia gravis.
- Severe hepatic impairment.

Diazepam Injection should not be used for the primary treatment of chronic psychosis. It 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

Except in emergencies, a second person should always be present during the intravenous use of diazepam and facilities for resuscitation should always be available. Patients should ideally 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.

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, hyper osmolality, 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.

The elderly, and patients with impaired renal and/or hepatic function may be particularly susceptible to the adverse effects of diazepam listed. Dose reduction may be required.

Extreme care must be taken when administering diazepam injection to very ill patients and to those with limited pulmonary reserve, because of the possibility of respiratory depression or apnoea.

Use with caution in patients with myasthenia gravis, porphyria, known history of drug or alcohol abuse, or organic brain changes, particularly arteriosclerosis. Diazepam injection should be

administered with caution to patients in whom a drop in blood pressure might lead to cardiovascular or cerebrovascular complications.

The dependence potential of diazepam increases with dose and duration of treatment and is greater in patients with a history of alcohol or drug abuse. Withdrawal symptoms may occur.
with benzodiazepines following normal use of therapeutic doses for only short periods and may be associated with physiological and psychological sequelae (see section 4.8 Withdrawal effects). The potential for withdrawal symptoms should be considered when treating patients for more than a few days; abrupt discontinuation should be avoided and the dose reduced gradually.
Abuse of diazepam has been reported.

Diazepam may induce anterograde amnesia. This occurs most often several hours after administration. In cases of loss or bereavement, psychological adjustment may be inhibited by benzodiazepines.

Paradoxical reactions and disinhibition have been occasionally reported during benzodiazepine use. Such reactions may be more likely to occur in children and the elderly. Should these occur, use of the drug should be discontinued (see Undesirable Effects). Extreme caution should be used in prescribing diazepam for patients with personality disorders. Suicide may be precipitated in patients who are depressed, as may aggressive behaviour towards self and others.

4.5 Interaction with other medicinal products and other forms of interaction

Centrally Acting Agents

If **VERZEPAM** is to be combined with other centrally acting agents careful consideration should be given to the pharmacology of the agents employed particularly with compounds that may potentiate or be potentiated by the action of **VERZEPAM**, such as phenothiazines, antipsychotics, anxiolytics/sedatives, hypnotics, anticonvulsants, narcotic analgesics, anesthetics, sedative antihistamines, narcotics, barbiturates, MAO inhibitors and other antidepressants.

Alcohol

Concomitant use with alcohol is not recommended due to enhancement of the sedative effect.

Antacids

Diazepam peak concentrations are 30% lower when antacids are administered concurrently. However, there is no effect on the extent of absorption. The lower peak concentrations appear due to a slower rate of absorption, with the time required to achieve peak concentrations on average 20 - 25 minutes greater in the presence of antacids. However, this difference was not statistically significant.

Compounds Which Inhibit Certain Hepatic Enzymes

There is a potentially relevant interaction between diazepam and compounds which inhibit certain hepatic enzymes (particularly cytochrome P450 3A and 2C19). Data indicate that these compounds influence the pharmacokinetics of diazepam and may lead to increased and prolonged sedation. At present, this reaction is known to occur with cimetidine, ketoconazole, fluvoxamine, fluoxetine, and omeprazole.

Phenytoin

There have also been reports that the metabolic elimination of phenytoin is decreased by diazepam.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In studies in which mice and rats were administered diazepam in the diet at a dose of 75 mg/kg/day (approximately 6 and 12 times, respectively, the maximum recommended human dose [MRHD=1 mg/kg/day] on a mg/m2 basis) for 80 and 104 weeks, respectively, an increased incidence of liver tumors was observed in males of both species. The data currently available are inadequate to determine the mutagenic potential of diazepam. Reproduction studies in rats showed decreases in the number of pregnancies and in the number of surviving offspring following administration of an oral dose of 100 mg/kg/day (approximately 16 times the MRHD on a mg/m2 basis) prior to and during mating and throughout gestation and lactation. No adverse effects on fertility or offspring viability were noted at a dose of 80 mg/kg/day (approximately 13 times the MRHD on a mg/m2 basis).

Pregnancy

An increased risk of congenital malformations and other developmental abnormalities associated with the use of benzodiazepine drugs during pregnancy has been suggested. There may also be non-teratogenic risks associated with the use of benzodiazepines during pregnancy. There have

been reports of neonatal flaccidity, respiratory and feeding difficulties, and hypothermia in children born to mothers who have been receiving benzodiazepines late in pregnancy. In addition, children born to mothers receiving benzodiazepines on a regular basis late in pregnancy may be at some risk of experiencing withdrawal symptoms during the postnatal period.

Diazepam has been shown to be teratogenic in mice and hamsters when given orally at daily doses of 100 mg/kg or greater (approximately eight times the maximum recommended human dose [MRHD=1 mg/kg/day] or greater on a mg/m2 basis). Cleft palate and encephalopathy are the most common and consistently reported malformations produced in these species by administration of high, maternally toxic doses of diazepam during organogenesis. Rodent studies have indicated that prenatal exposure to diazepam doses similar to those used clinically can produce long-term changes in cellular immune responses, brain neurochemistry, and behavior.

In general, the use of diazepam in women of childbearing potential, and more specifically during known pregnancy, should be considered only when the clinical situation warrants the risk to the fetus. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Patients should also be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physician about the desirability of discontinuing the drug.

Labor and Delivery

Special care must be taken when **VERZEPAM** is used during labor and delivery, as high single doses may produce irregularities in the fetal heart rate and hypotonia, poor sucking, hypothermia, and moderate respiratory depression in the neonates. With newborn infants it must be remembered that the enzyme system involved in the breakdown of the drug is not yet fully developed (especially in premature infants).

Nursing Mothers

Diazepam passes into breast milk. Breastfeeding is therefore not recommended in patients receiving **VERZEPAM.**

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 6 months have not been established.

Geriatric Use

In elderly patients, it is recommended that the dosage be limited to the smallest effective amount to preclude the development of ataxia or oversedation (2 mg to 2.5 mg once or twice daily, initially to be increased gradually as needed and tolerated).

Extensive accumulation of diazepam and its major metabolite, desmethyldiazepam, has been noted following chronic administration of diazepam in healthy elderly male subjects. Metabolites of this drug are known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Hepatic Insufficiency

Decreases in clearance and protein binding, and increases in volume of distribution and half-life have been reported in patients with cirrhosis. In such patients, a 2- to 5- fold increase in mean half-life has been reported. Delayed elimination has also been reported for the active metabolite desmethyldiazepam. Benzodiazepines are commonly implicated in hepatic encephalopathy. Increases in half-life have also been reported in hepatic fibrosis and in both acute and chronic hepatitis .

4.6 Pregnancy and lactation

Pregnancy:

There is no evidence as to drug safety 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.

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.

Lactation:

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

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

Most frequently reported adverse reactions associated with benzodiazepines include daytime drowsiness, sedation, unsteadiness and ataxia; these are dose-related and may persist to the following day.

Blood and lymphatic system disorders:

Very rare reports of thrombocytopenia, leucopenia, agranulocytosis

Immune system disorders:

Hypersensitivity reactions, including anaphylaxis

Metabolism and nutrition disorders:

Metabolic disorders including metabolic acidosis, increased anion gap and hyperosmolality have been reported as a consequence of propylene glycol toxicity (see section 4.4 Special warnings and precautions for use).

Psychiatric disorders:

Confusion, depression and unmasking of depression, numbed emotions, disinhibition, euphoria, appetite changes, sleep disturbance, change in libido, dependence, suicidal ideation/attempt. Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, rage, insomnia, nightmares, hallucinations, psychoses, sexual arousal, and inappropriate behaviour are known to occur with benzodiazepines including diazepam. These are more likely to occur in children and the elderly.

Nervous system disorders:

Daytime drowsiness, sedation, dizziness, ataxia, tremor, headache, reduced alertness, dysarthria/slurred speech, transient anterograde amnesia or memory impairment.

Eye disorders:

Visual disturbance.

Ear and labyrinth disorders:

Vertigo.

Vascular disorders:

Hypotension may occur. The incidence of hypotension may be reduced by not exceeding the recommended rate of administration. Patients should be managed in the supine position and kept there throughout the procedure.

Intravenous injections of diazepam may be associated with local reactions and thrombophlebitis and venous thrombosis may occur.

Respiratory thoracic and mediastinal disorders:

Apnoea, respiratory depression, particularly with high doses (see 4.9 Overdose). Worsening of sleep apnoea, worsening of obstructive pulmonary disease.

Gastrointestinal disorders:

Gastrointestinal disturbances (nausea, salivation changes).

Hepatobiliary disorders:

Raised liver function test values, jaundice.

Skin and subcutaneous tissue disorders:

Rash, allergic dermatitis, urticaria.

Musculoskeletal disorders:

Muscle weakness.

Renal and urinary disorders:

Urinary retention, incontinence

General disorders:

Fatigue, injection site pain or irritation (see Vascular disorders)

Drug withdrawal symptoms:

Symptoms reported following discontinuation of benzodiazepines include headaches, muscle pain, anxiety, depression, insomnia, restlessness, confusion, irritability, sweating, and the occurrence of rebound phenomena.

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 *Symptoms:*

The symptoms of a mild overdose may include confusion, somnolence, lethargy, impairment of consciousness, diminished reflexes or paradoxical excitation. In more serious cases, and especially when other CNS-depressant drugs or alcohol are ingested, symptoms may include ataxia, hypotension, hypotonia, respiratory depression, coma and, very rarely, death.
Rarely, propylene glycol toxicity has been reported following higher than recommended doses (see section 4.4 Special warnings and precautions for use).

Treatment:

Treatment is symptomatic. Respiration, heart rate, blood pressure and body temperature should be monitored and supportive measures taken to maintain cardiovascular and respiratory function.
Hypotension may be controlled if necessary by IV administration of adrenaline (epinephrine).
Benzodiazepines are poorly dialysable.

The benzodiazepine antagonist, flumazenil, may be useful in hospitalised patients for the management of benzodiazepine overdose. 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group (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

premedicant, 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 highly lipid soluble and crosses the blood brain barrier. These properties quallify it for intravenous use in short term anaesthetic procedures since it acts promptly on the brain, and its initial effects decrease rapidly as it is distributed into fat deposits and tissues.Following the administration of an adequate intravenous dose of diazepam, effective plasma concentration are usually reached within 5 minutes ca.150-400mg/ml.,

Absorption is erratic following intramuscular administration and lower peak plasma concentration, may be obtained than those following oral administration.

Diazepam is exensively protein bound (95-99%). The volume of distribution is between 0.95 and 21/ kg depeding on age.Diazepam and its main metabolites,N-desmethyldiazepan ,cross the placenta and are secreted in breast milk.

Diazepam is metabolised predominately in the liver. Its metabolites, Ndesmethyldiazepam(nordiazepam), temazepam and oxazepam, which appear in the urine as glucuronides, are also pharmacologically active substances. Only 20% of the metabolites are detected in the urine in first 72 hours.

Diazepam has a biphasic half life with an initial rapid distribution phase followed by a prolonged terminal elimination phase of 1-2 days. For the active metabolites N-desmethyldiazepam, temazepam and oxazepam, the half lives are 30-100 hours, 10-20 hours and 5-15 hours,respectively.

Excreation is mainly renal and also partly biliary. It is dependent on age as well as hepatic and renal function.

Metabolism and elimination in the neonate are markedly slower than in children and adults In the elderly, elimination is prolonged by a factor of 2 to 4. In patients with impaired renal function,

elimination is also prolonged. In patients with hepatic disorders (liver cirrhosis hepatitis), elimination is prolonged by a factor of 2.

5.3 Preclinical safety data

Preclinical safety data does not add anything of further significance to the prescriber.

6. Pharmaceutical particulars

6.1 List of excipients Benzyl alcohol BP

Propylene glycol BP

Ethyl alcohol BP

Disodium EDTA BP

Sodium benzoate BP

Benzoic acid BP

Water for injection BP

6.2 Incompatibilities None known.

6.3 Shelf life 24 Months.

6.4 Special precautions for storage

The product must be stored at a temperature not exceeding 30°C. Protect from light.

6.5 Nature and contents of container

Primary Packing – USP Type- I amber color glass Ampoule

Secondary Packing- Printed Carton & Tray

Tertiary Packing- i. Corrugated Box

- 10x2ml amber color ampoules loading on a plastic tray.
- 10x2ml Tray loaded amber color ampoules in an inner Printed Carton.
- 10x10x2ml amber color ampoules packing in an Outer Printed Carton or in a Shrink Wrap.

This container closure system is suitable for storage, efficacy, transportation and use of the finished product.

PACK SIZE:

10x10x2ml.

6.6 Special precautions for disposal and other handling

For single use only. Discard any unused product at the end of each operating session.

7. Registrant

Generic Africa Limited
Aqua Office Suites,
5th Floor Murang'a Road,
P.O. BOX 14793-00400, Kenya

8. Manufacturer

Verve Human Care Laboratories
15-A, Pharmacity, Selaqui,
Dehradun-248011
India

9. Date of revision of the text

Not applicable

10. Dosimetry (If Applicable)

Not applicable

11. Instructions for preparations of Radiopharmaceuticals (if Applicable)

Not applicable

1.17.2 Patient Information Leaflet

Not Applicable as this Product is subjected to medical prescription:

o Controlled Drug Substance o Prescription Only Medicine, POM