Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

VERZEPAM 5 mg

2. Qualitative and quantitative composition

Each uncoated tablet contains Diazepam BP 5 mg

This product contains lactose.

For a full list of excipients, see section 6.1

3. Pharmaceutical form

Uncoated tablet
White coloured, elongated, biconvex, uniscored, uncoated tablets.

4. Clinical particulars

4.1 Therapeutic indications

Adults

1) The short-term relief (2-4 weeks) only, of anxiety which is severe, disabling, or subjecting the individual to unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic or psychotic illness.
2) Cerebral palsy.
3) Muscle spasm.
4) As an adjunct to certain types of epilepsy (*eg* myoclonus).
5) Symptomatic treatment of acute alcohol withdrawal.
6) As oral premedication for the nervous dental patient.
7) For premedication before surgery

Children

1) Control of tension and irritability in cerebral spasticity in selected cases
2) As an adjunct to the control of muscle spasm in tetanus
3) Oral premedication (see section 4.4)

4.2 Posology and method of administration

As an anxiolytic, the lowest effective dose should be employed; dosage regimes should not exceed beyond 4 weeks and treatment should be gradually withdrawn. Patients who have received benzodiazepines for a long time may require an extended withdrawal period. Long-term chronic use is not recommended.

Adults:

Anxiety states, obsessive-compulsive neuroses, and other psychiatric disorders: 5-30mg daily in divided doses.

Insomnia associated with anxiety: 5-15mg before retiring.
Cerebral palsy: 5-60mg daily in divided doses.
Upper motor neuronic spasticity: 5-60mg daily in divided doses.
Muscle spasm of varied aetiology, fibrositis, cervical spondylosis: 5-15mg daily in divided doses.
Adjunct to the management of some types of epilepsy: 2-60 mg daily in divided doses.
Alcohol withdrawal: 5-20mg, repeated if necessary in 2 to 4 hours.
Oral premedication in dental patients: 5mg the night before, 5mg on waking and 5mg two hours before the appointment.
Oral Premedication before surgery: 5mg-20mg.
Children:
Alternative presentations of diazepam are recommended for paediatric usage in order to obtain suitable doses of less than 5mg.
Spastic children with minimal brain damage: 5-40mg daily in divided doses.
Oral Premedication before surgery: 2mg-10mg Elderly and debilitated patients:
Doses should be half the above recommended doses.
Renal and hepatic impairment:
The use of diazepam in hepatic impairment may precipitate coma, therefore the dose should be reduced or an alternative drug considered. In severe renal impairment the dose should be reduced.

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.

Method of Administration: For oral administration.

4.3 Contraindications

Known hypersensitivity to benzodiazepines

- Phobic or obsessional states; chronic psychosis, hyperkinesis (paradoxical reactions may occur)
- Acute pulmonary insufficiency; respiratory depression, acute or chronic severe respiratory insufficiency (ventilatory failure may be exacerbated)
- Myasthenia gravis (condition may be exacerbated)
- Sleep apnoea (condition may be exacerbated)
- Severe hepatic insufficiency (elimination half-life of diazepam may be prolonged)
- Acute porphyria
- Diazepam should not be used as monotherapy in patients with depression or those with anxiety and depression as suicide may be precipitated in such patients.
- Planning a pregnancy.
- Pregnancy (unless there are compelling reasons).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

If **Verzepam** is to be combined with other psychotropic agents or anticonvulsant drugs, careful consideration should be given to the pharmacology of the agents to be employed – particularly with known compounds that may potentiate the action of diazepam, such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants .

The usual precautions are indicated for severely depressed patients or those in whom there is any evidence of latent depression or anxiety associated with depression, particularly the recognition that suicidal tendencies may be present and protective measures may be necessary.

Psychiatric and paradoxical reactions are known to occur when using benzodiazepine. Should this occur, use of the drug should be discontinued. These reactions are more likely to occur in children and the elderly.

A lower dose is recommended for patients with chronic respiratory insufficiency, due to the risk of respiratory depression.

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

In debilitated 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).
Some loss of response to the effects of benzodiazepines may develop after repeated use of **Verzepam** for a prolonged time.

Information for Patients

To assure the safe and effective use of benzodiazepines, patients should be informed that, since benzodiazepines may produce psychological and physical dependence, it is advisable that they consult with their physician before either increasing the dose or abruptly discontinuing this drug. The risk of dependence increases with duration of treatment; it is also greater in patients with a history of alcohol or drug abuse.
Patients should be advised against the simultaneous ingestion of alcohol and other CNSdepressant drugs during **Verzepam** therapy. As is true of most CNS-acting drugs, patients receiving **Verzepam** should be cautioned against engaging in hazardous occupations requiring complete mental alertness, such as operating machinery or driving a motor vehicle.

Warnings

Verzepam (Diazepam Tablet BP) is not recommended in the treatment of psychotic patients and should not be employed instead of appropriate treatment.
Since **Verzepam** (Diazepam Tablet BP) has a central nervous system depressant effect, patients should be advised against the simultaneous ingestion of alcohol and other CNS-depressant drugs during **Verzepam** (Diazepam Tablet BP) therapy.
As with other agents that have anticonvulsant activity, when **Verzepam** is used as an adjunct in treating convulsive disorders, the possibility of an increase in the frequency and/or severity of grand mal seizures may require an increase in the dosage of standard anticonvulsant medication. Abrupt withdrawal of **Verzepam** (Diazepam Tablet BP) in such cases may also be associated with a temporary increase in the frequency and/or severity of seizures.

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.

4.6 Pregnancy and Lactation

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**.

4.7 Effects on ability to drive and use machines

Sedation, amnesia and impaired muscular function may adversely effect the ability to drive or use machines. If insufficient sleep occurs, the likelihood of impaired alertness may be increased.

Impaired function and sedation may occur the following morning and for several days after. Patients should be warned that effects on the central nervous system may persist into the day after administration even after a single dose.

4.8 Undesirable effects

During the first week of administration or when high doses are used they may have a sedative effect and cause some degree of drowsiness. In such cases there is an advantage in administering half the total daily intake at night, the remainder being given in divided doses during the day. The elderly and debilitated are particularly sensitive to the effects of central depressant drugs and may experience confusion, especially if organic brain changes are present; the dosage of diazepam should not exceed one-half that recommended for other adults.

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Skin and appendages disorders
Allergic reactions (skin rash or itching) occur rarely.
Central and peripheral nervous disorders
Drowsiness, sedation, unsteadiness, ataxia is common (these effects are dose-related and may persist into the following day even after a single dose), light-headedness, headache, vertigo, dystonic effects occur rarely. Impaired motor ability, dizziness, muscle weakness, tremor, slurred speech.

Vision disorders
Visual disturbances occur rarely.
Psychiatric disorders
Libido fluctuations occur rarely. Anterograde amnesia (amnesia may be associated with inappropriate behaviour), concentration difficulties, abnormal psychological reactions, behavioural adverse effects include paradoxical aggressive outbursts, excitement, confusion, restlessness, agitation, irritability, delusions, rages, nightmares, hallucinations, psychoses, inappropriate behaviour, numbed emotions, the uncovering of depression with suicidal tendencies and dependence. Abuse of benzodiazepines has been reported.
Gastro-intestinal system disorders
Gastrointestinal upsets occur rarely. Increased salivary secretion.
Liver and billiary system disorders Jaundice occurs rarely.
Endocrine disorders Gynaecomastia.
Cardio disorders
Hypotension occurs rarely.
Respiratory system disorders
Respiratory depression, apnoea.
Blood disorders
Blood dyscrasias occur rarely.
Urinary system disorders
Urinary retention occurs rarely. ***Body as a whole-general disorders*** Fatigue, anaphylaxis.
Withdrawal effects
Withdrawal symptoms: Development of dependence is common after regular use, even in therapeutic doses for short periods, particularly in patients with a history of drug or alcohol abuse or marked personality disorders. Discontinuation of the therapy may result in withdrawal or rebound phenomena (see 4.4 Special Warnings and Special Precautions for Use). Symptoms of benzodiazepine withdrawal include anxiety, depression, impaired concentration, insomnia, headache, dizziness, tinnitus, loss of appetite, tremor, perspiration, irritability, perceptual disturbances such as hypersensitivity to physical, visual, and auditory stimuli and abnormal taste, nausea, vomiting, abdominal cramps, palpitations, mild systolic hypertension, tachycardia, and orthostatic hypotension.

Rare and more serious symptoms include muscle twitching, confusional or paranoid psychosis, convulsions, hallucinations, and a state resembling delirium tremens. Broken sleep with vivid dreams and increased REM sleep may persist for some weeks after withdrawal of benzodiazepines

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poison board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org.

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, cardio-respiratory 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. Management
Maintain a clear airway and adequate ventilation.
Consider activated charcoal (50g for an adult, 1g/kg for a child) in adults who have taken more than 100mg or children who have taken more than 1mg/kg within one hour, provided they are not too drowsy.
Monitoring 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 not significantly removed from the body by dialysis.

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 be suppressing seizures induced by the second drug; its antagonism by flumazenil can reveal severe status epilepticus that is very difficult to control.

Contraindications to the use of flumazenil include features suggestive of a tricyclic antidepressant ingestion including a wide QRS, or large pupils. Use in patients post-cardiac 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 behavioral 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 Pharmacodynamic properties

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 qualify 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, N-desmethyldiazepam (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

There are no preclinical safety data of relevance to the prescriber.

6. Pharmaceutical Particulars

6.1 List of Excipients

Microcrystalline Cellulose BP, Starch BP, Di basic Calcium Phosphate BP, Lactose Monohydrate BP, Starch for Paste BP, PVPK-30 BP, Methyl Paraben Sodium BP, Propyl Paraben Sodium BP, Purified water BP, Talcum BP, Magnesium Stearate BP, Sodium Starch Glycolate BP, Colloidal Silicon Dioxide BP, Sodium Lauryl Sulphate BP.

6.2 Incompatibilities

None Known

6.3 Shelf-Life

3 Years

6.4 Special Precautions for storage

Store at a temperature not exceeding 30°C. Protect from light and moisture.

6.5 Nature and Content of container

10 tablets are packed in amber color Alu/PVC blister pack, such a 5 or 10 or 3 such blisters are packed as a single combo pack along with a pack insert.

6.6 Special precautions for disposal and other handling

Use as directed by a physician

7. Marketing Authorization Holder

Verve Human Care Laboratories,
15-A, Pharmacity, Selaqui, Dehradun-248011 Uttarakhand,
Telephone No.: 91-135-2698248, 2699996, 2699997, 2699998

8. Marketing Authorization Number

CTD10526

9. Date of first authorization/renewal of the authorization

20/11/2023

10. Date of revision of the text

06/05/2025