DIAZEPAM

USP Injection

10 mg/2 ml (5 mg/ml)

COMPOSITION:
Each ml contains:
Diazepam USP ..... 5 mg
Benzyl Alcohol USP ..... 1.5% v/v
(as a preservative)
Water for Injection USP ..... q.s.

THERAPEUTIC INDICATIONS:
Diazepam is a long-acting benzodiazepine possessing anticonvulsant, anxiolytic, muscle relaxant, and amnesic properties. It is used for the short-term treatment of severe anxiety disorders; as a hypnotic for the short-term treatment of insomnia; as a sedative during minor surgeries and as pre-medication prior to general anesthesia; as an anticonvulsant to control muscle spasms; and in the treatment of drug withdrawal syndromes.

PHARMACOKINETICS AND PHARMACODYNAMICS:
Diazepam is rapidly and completely absorbed from the digestive tract.
Peak plasma concentration is reached 30 to 90 minutes after oral administration; following rectal administration, the maximum concentration is reached between 10 and 30 minutes, whereas intravenous administration results in a faster onset. Intramuscular administration may be erratic, resulting in a lower peak plasma concentration compared to oral administration.
Diazepam is highly lipid-soluble and crosses the blood-brain barrier. It acts rapidly on the brain, and its initial effects diminish quickly as the drug is redistributed into fat stores.
Diazepam has a biphasic half-life, characterized by an initial rapid distribution phase followed by a prolonged terminal elimination phase of 1 to 2 days. Diazepam and desmethyldiazepam are transferred from mother to infant via breast milk.
Diazepam undergoes extensive hepatic metabolism; in addition to desmethyldiazepam, its active metabolites include oxazepam and temazepam. It is excreted in the urine, primarily in free form or as conjugated metabolites. Diazepam is 98–99% bound to plasma proteins.

CONTRAINDICATIONS:
Administration of diazepam should be avoided in patients with pre-existing CNS depression or in cases of coma, respiratory depression, respiratory insufficiency, or sleep apnea; it should be used with caution in patients with chronic respiratory insufficiency.
It should be administered with caution to the elderly or frail patients, who may be more prone to developing adverse effects.
Caution is required in patients with muscle weakness or hepatic or renal disorders.
Diazepam is not recommended for the treatment of chronic psychoses or severe phobic states. Diazepam-induced disinhibition may precipitate suicide or aggressive behavior; therefore, it should not be used as the sole medication for treating depression or anxiety associated with depression.

RESTRICTIONS ON USE DURING PREGNANCY AND BREASTFEEDING:
Use of diazepam during the first trimester of pregnancy and during labor may result in consequences such as neonatal withdrawal syndrome or "floppy infant syndrome"; therefore, it is preferable not to administer it to pregnant women. Although the excretion of diazepam into breast milk does not pose a danger to the infant's feeding, the situation must be monitored to avoid sedation and an inability to breastfeed; consequently, the administration of benzodiazepines to breastfeeding mothers is not recommended.

SECONDARY AND ADVERSE REACTIONS:
The most frequent adverse effects of diazepam are drowsiness, sedation, and ataxia, which occur as a consequence of CNS depression and diminish with continued administration.
Less common effects include vertigo, headache, confusion, depression, slurred speech, libido disturbances, tremor, visual disturbances, urinary retention or incontinence, gastrointestinal disorders, changes in salivation, and amnesia; some patients may experience excitation that can lead to hostility, aggression, and disinhibition. Reactions such as jaundice, bleeding disorders, and hypersensitivity have rarely been reported.
Intravenous administration may cause pain and thrombophlebitis; increases in serum liver enzyme levels have also occurred.
An overdose of diazepam can produce CNS depression and coma or paradoxical excitation. However, death is rare when the drug is administered alone.
Administration of diazepam during the first trimester of pregnancy has occasionally been linked to congenital malformations in the infant, but there is no clear correlation.

PRECAUTIONS REGARDING CARCINOGENESIS, MUTAGENESIS, TERATOGENESIS, AND EFFECTS ON FERTILITY:
The International Agency for Research on Cancer concluded that there is insufficient evidence from human studies to conclude that diazepam does not cause breast cancer.

DRUG AND OTHER INTERACTIONS:
Increased sedation or respiratory or cardiovascular depression may occur if diazepam or another benzodiazepine is administered with other CNS depressants, including alcohol, antidepressants, antihistamines, antipsychotics, general anesthetics, other hypnotics or sedatives, and opioid analgesics.
The sedative effect of benzodiazepines may also be enhanced by cisapride.
Adverse effects may occur due to the simultaneous administration of other drugs that interfere with benzodiazepine metabolism, including analgesics, general anesthetics, calcium channel blockers, antiarrhythmics, antibacterials, anticoagulants, oral decongestants, antidepressants, antiepileptics, antivirals, neuromuscular blocking agents, cyclosporine, clonidine, clozapine, corticosteroids, digoxin, disulfiram, gastrointestinal drugs, penicillamine, probenecid, smooth muscle relaxants, tobacco, and xanthines.

CHANGES IN LABORATORY TEST RESULTS:
It has been reported that values for transaminases, alkaline phosphatase, gamma-glutamyl transpeptidase, and glucose may be altered, as well as thyroid function tests.

GENERAL PRECAUTIONS:
The sedative effects of diazepam are most pronounced during the first few days of administration. Affected patients should not drive or operate machinery. Monitoring of cardiorespiratory function is recommended when benzodiazepines are used for deep sedation. Regular use of diazepam causes dependence, even at therapeutic doses and over short periods. Diazepam should be used with caution in patients with a history of alcoholism or drug dependence due to the risk of dependence. Intravenous administration is recommended only when means are available to reverse respiratory depression. Patients should remain in a supine position under medical supervision.

DOSAGE AND ROUTE OF ADMINISTRATION:
Deep intramuscular or slow intravenous. Given that diazepam carries a risk of dependency—a factor that significantly influences dosage and treatment duration—doses should be kept as low as possible while still controlling symptoms. The treatment period should be short, generally not exceeding four weeks, and the drug should be withdrawn gradually. Intravenous injection must be administered slowly into a large vein in the antecubital fossa at a rate of 5 mg/min (1 mL). Diazepam may also be administered via continuous intravenous infusion.
Due to the risk of diazepam precipitation, freshly prepared solutions must be used in accordance with the manufacturer's instructions. Do not use PVC or cellulose propionate equipment; suitable materials for administration include glass, polyolefin, polypropylene, and polyethylene.
For severe anxiety, the intramuscular or intravenous dose is 10 mg, which may be repeated after 4 hours if necessary. For premedication prior to intravenous general anesthesia, the usual adult dose is 100 to 200 µg/kg; use in children is not recommended.
For sedation during minor surgery, an intravenous dose of 10 to 20 mg administered over 2 to 4 minutes is recommended.
For seizures, intravenous diazepam may be used in adults as an alternative treatment at doses of 10 to 20 mg (administered at a rate of 5 mg/min), repeated after 60 minutes if necessary. Once the seizure is controlled, a slow infusion of 3 mg/kg may be administered over 24 hours. In children, the intravenous or intramuscular dose is 200 to 300 µg/kg or 1 mg per year of age.

MANIFESTATIONS AND MANAGEMENT OF OVERDOSE OR ACCIDENTAL INGESTION:
Diazepam overdose typically manifests as central nervous system depression, causing drowsiness and potentially progressing to coma. In mild cases, it presents as drowsiness, lethargy, and mental confusion.
In severe cases, ataxia, depressed mood, hypotension, and respiratory depression occur.
In very rare cases, coma and death.
Treatment: In cases of parenteral overdose, the benzodiazepine antagonist (flumazenil) should be used at doses of 0.1 to 0.3 mg/min, without exceeding a total dose of 1 to 2 mg.

PRESENTATIONS:
Box containing 10 vials (2 mL) with 10 mg.

STORAGE RECOMMENDATIONS:
Store at temperatures below 30°C. Protect from light. Keep out of the reach of children.

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