SEREPAM

Ampoule

Composition
Each ampoule of 2 ml contains Diazepam 10 mg.

Action
Diazepam is a benzodiazepine tranquillizer that is believed to act by facilitating the synaptic actions of gamma aminobutyric acid (GABA). GABA is one of the major inhibitory neurotransmitters of the CNS. Diazepam does not act at the same site as GABA, but at a presumably allosterically linked site, called the benzodiazepine receptor. It is through this site that the anticonvulsant, sedative, skeletal muscle relaxant, and amnestic properties of diazepam are mediated.

Pharmacokinetics
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 concentrations are usually reached within 5 minutes (ca. 150-400 ng/ml).

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

Diazepam is extensively protein bound (95-99%). The volume of distribution is between 0.95 and 2 l/kg depending on age. Diazepam and its main metabolite, N-desmethyldiazepam, cross the placenta and are secreted in breast milk.

Diazepam is metabolised predominantly 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 the 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.

Excretion 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.

Indications
- Symptomatic relief of tension and anxiety, either alone or when associated with stressful situations.
- Psychoneurotic states manifested by tension, anxiety, apprehension, fatigue and depressive symptoms.
- In acute alcohol withdrawal, Serepam may be useful in the symptomatic relief of tremor, impending or acute delirium tremens and hallucinosis.
- Serepam is a useful adjunct in the relief of skeletal muscle spasm, spasticity, stiff-man syndrome and tetanus.
- When used intravenously, Serepam injection is a useful adjunct in status epilepticus and severe recurrent convulsive seizures.

- Premedication in patients undergoing surgical procedures (the intramuscular route is preferred), or in patients undergoing cardioversion (the intravenous route is preferred).

Contraindications

- Known hypersensitivity to benzodiazepines.
- Acute pulmonary insufficiency, psychoses.
- First trimester of pregnancy and in breastfeeding.
- Acute narrow-angle glaucoma (benzodiazepines may be used in patients with open-angle glaucoma who are receiving appropriate therapy).
- Diazepam injection should not be administered to patients in shock, coma, or acute alcoholic intoxication with depression of vital signs.

Warnings

Parenteral (I.M. or I.V.) therapy is indicated primarily in acute states. When used intravenously, Diazepam should be injected slowly, taking at least 1 minute for each 5 mg (1 ml) administered. Small veins should be avoided. Patients should be kept under observation, preferably in bed, for up to 3 hours.

Following an injection, ambulatory patients should not be permitted to engage in potentially dangerous activities requiring mental alertness, such as driving a car or operating machinery. The same precaution applies to childhood activities, such as bicycle riding and playing near traffic. Diazepam should not be injected intra-arterially, as this may produce arteriospasm resulting in gangrene, which may require amputation.

Diazepam should be administered parenterally with extreme care (particularly I.V.) to the elderly or very ill, and to those with limited pulmonary reserve. Because of the possibility of apnea or cardiac arrest, resuscitative facilities should be available. Diazepam injection is not recommended for obstetric use. Tonic status epilepticus has been precipitated in patients treated with I.V. diazepam for petit mal or petit mal variant status.

Laryngospasm, increased cough reflex, depressed respiration, dyspnea, hyperventilation, and pain in the throat or chest have been reported during peroral endoscopic procedures. Topical anaesthetics should be used. Hypotension or muscular weakness is possible, particularly when benzodiazepines are used with narcotics, barbiturates or alcohol.

Although seizures may be brought under control promptly, a significant proportion of patients experience a return to seizure activity, presumably due to the short-lived effect of diazepam after intravenous administration. The physician should be prepared to re-administer the drug. However, Diazepam is not recommended for maintenance, and once seizures are brought under control, consideration should be given to the administration of agents useful in longer-term control of seizures.

Prolonged use may cause dependence.
Withdrawal symptoms similar in character to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of benzodiazepine drugs. These symptoms include convulsions, tremor, abdominal and muscle cramps, vomiting and sweating. When discontinuing therapy in patients who have used these agents for prolonged periods, dosage should be decreased gradually to avoid the possibility of withdrawal symptoms.

Pregnancy
Category C
Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Use in Labor and Delivery

Benzodiazepines have been found in maternal and cord blood, indicating placental transfer of the drug. Therefore, benzodiazepines are not recommended for obstetrical use. Neonatal withdrawal, consisting of severe tremulousness and irritability, as well as neonatal flaccidity and respiratory problems, has been attributed to maternal ingestion of benzodiazepines.

Use during labor has resulted in a "floppy infant" syndrome, manifested by hypotonia, lethargy and sucking difficulties. Prolonged CNS depression has been observed in neonates, apparently due to inability to biotransform diazepam into inactive metabolites.

Nursing Mothers
Benzodiazepines are excreted in breast milk. Since neonates metabolize this drug more slowly than adults do, and accumulation of the drug and its metabolites to toxic levels is possible, it should not be administered to nursing women.

Use in Neonates and Premature Infants
Since Diazepam injection contains benzyl alcohol, it should not be administered to neonates and premature infants.

Paediatric Use
In order to obtain maximal clinical effect with the minimum amount of drug, and thus reduce the risk of hazardous side effects such as apnea or prolonged periods of somnolence, it is recommended that the drug be given slowly over a 3-minute period, at a dosage not exceeding 0.25 mg/kg body weight. After an interval of 15-30 minutes, the initial dosage can be safely repeated. However, if relief of symptoms is not obtained after a third administration, adjunctive therapy appropriate to the condition being treated is recommended.

Adverse Reactions
In common with other benzodiazepines, the following side effects have occasionally been reported: drowsiness, fatigue, ataxia, hypotension, gastrointestinal disturbances, visual disturbances, skin rash, urinary retention, headache, confusion, vertigo, and change in libido, blood dyscrasias, jaundice, and paradoxical reactions such as acute hyperexcitation states.

Drowsiness and fatigue, if they occur, are usually observed at the beginning of therapy. They usually diminish on continued medication or upon lowering of the dose.
Venous thrombosis and phlebitis may be encountered at the site of injection.

Precautions
Although hypotension has rarely occurred, the drug should be administered with caution to patients in whom a drop in blood pressure might lead to cardiac complications.
The usual precautions in treating patients with impaired hepatic function should be observed.

The kidney excretes metabolites of diazepam. To avoid excess accumulation, caution should be exercised in administration to patients with compromised kidney function.
If use in patients with seizure disorders results in an increased frequency or severity of grand mal seizures, it may be necessary to increase the dosage of standard anticonvulsant medication.

Drug Interactions
Diazepam/ Cimetidine/ Oral Contraceptives/ Disulfiram/ Fluoxetine/ Isoniazid/ Ketoconazole/ Metoprolol/ Propoxyphene/ Propranolol/ Valproic Acid

These drugs, due to inhibition of hepatic metabolism, may decrease the elimination of diazepam that undergoes oxidative hepatic metabolism. The pharmacological effects of diazepam may be increased and excessive sedation/ impaired psychomotor function may occur.

Diazepam/ Alcohol/ Other CNS Depressants (e.g. barbiturates, narcotics)
Increased CNS effects (e.g. impaired psychomotor function, sedation) may occur.

Diazepam/ Digoxin
Serum concentrations of digoxin may be increased. Toxicity, characterized by gastrointestinal and neuropsychiatric symptoms and cardiac arrhythmias may occur.
Digoxin serum levels should be monitored.

Diazepam/ Levodopa
Co-administration may decrease the antiparkinson efficacy of levodopa.

Diazepam/ Probenecid
Probenecid may interfere with diazepam conjugation in the liver, possibly resulting in a more rapid onset or prolonged effect.

Diazepam/ Theophyllines
Theophyllines may antagonize the sedative effect of diazepam.

Dosage and Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
For intravenous administration, the drug should be injected slowly, at a maximum rate of 5 mg/min. Small veins (e.g. dorsum of hand or wrist) should not be used. Extreme care should be taken to avoid intra-arterial administration or extravasation.

If it is not feasible to administer Serepam directly I.V. it may be injected slowly through the infusion tubing, as close as possible to the vein insertion. When Serepam is administered intramuscularly, it should be injected deeply into the muscle.

Once the acute symptomatology has been controlled with injectable Serepam, patients may be placed on oral Serepam therapy, if further treatment is required. Dosage should be individualized for maximum beneficial effect.

The usual recommended dose in older children and adults ranges from 2-20 mg, I.M. or I.V., depending on the indication and its severity. In some conditions, larger doses may be required. In such cases, doses should be increased cautiously, to avoid adverse effects.

In acute conditions, the injection may be repeated within 1 hour, although an interval of 3-4 hours is usually satisfactory.
Lower doses (usually 2-5 mg), with a slow increase in dosage, should be used for elderly or debilitated patients, and when other sedative drugs are administered simultaneously.
Recommended doses as per specific indications are listed below:

Adults
Moderate Anxiety Disorders and Symptoms of Anxiety
2-5 mg, I.M. or I.V., Repeat after 3-4 hours, if necessary.

Severe Anxiety Disorders and Symptoms of Anxiety
5-10 mg, I.M. or I.V., Repeat after 3-4 hours, if necessary.

Acute Alcohol Withdrawal
Initially 10 mg, I.M. or I.V., then 5-10 mg after 3-4 hours, if necessary.

Endoscopic Procedures
The I.V. dosage should be titrated to the desired sedative response, such as slurring of speech, with slow administration immediately prior to the procedure. Usually 10 mg or less is adequate, but up to 20 mg, I.V. may be given, particularly when concomitant narcotics are omitted. If I.V. administration cannot be used, 5-10 mg should be given I.M. approximately 30 minutes prior to the procedure.

Muscle Spasm
Initially 5-10 mg, I.M. or I.V., then 5-10 mg after 3-4 hours, if necessary. For tetanus, larger doses may be required.

Status Epilepticus and Severe Recurrent Convulsive Seizures
Initially 5-10 mg (I.V. preferred). If necessary, this injection may be repeated at 10-15 minute intervals, up to a maximum dose of 30 mg.

Extreme caution must be exercised with individuals with chronic lung disease or unstable cardiovascular status.

Preoperative Medication
10 mg (I.M. preferred), before surgery.

Cardioversion
5-15 mg, I.V., within 5-10 minutes prior to the procedure.

Children
Since Serepam injection contains benzyl alcohol, this preparation should not be administered to neonates and premature infants.

To obtain maximum clinical effect with minimum amount of drug, and to reduce the risk of hazardous side effects such as apnea or prolonged periods of somnolence, the drug should be administered slowly over 3 minutes, not exceeding 0.25 mg/kg body weight. After an interval of 15-30 minutes, the initial dose can be repeated. If relief of symptoms is not obtained after a third dose, appropriate adjunctive therapy is recommended. Facilities for respiratory assistance should be readily available.

Muscle Spasm
For tetanus in infants over 30 days of age, administer 1-2 mg, I.M. or I.V., slowly, repeated every 3-4 hours, as necessary. In children 5 years or older, 5-10 mg, repeated every 3-4 hours, may be required to control tetanus spasms. Respiratory assistance should be available.

Status Epilepticus and Severe Recurrent Convulsive Seizures
In infants over 30 days of age and children less than 5 years, administer 0.2-0.5 mg, slowly, every 2-5 minutes, up to a maximum of 5 mg (I.V. preferred). In children 5 years or older, administer 1 mg every 2-5 minutes, up to a maximum of 10 mg (slow I.V. administration preferred). Repeat after 2-4 hours if necessary.
EEG monitoring of the seizure may be helpful.

Over Dosage
Manifestations
Manifestations include somnolence, confusion, coma and diminished reflexes. Respiration, pulse and blood pressure should be monitored, as in all cases of drug over dosage. However, in general, these effects have been minimal.

Treatment
General supportive measures should be employed along with intravenous fluids. An adequate air-way should be maintained. Hypotension may be combated by the administration of noradrenaline or metaraminol. Caffeine and sodium benzoate may be given to combat CNS-depressive effects. Dialysis is of limited value.

Pharmaceutical Precautions
Serepam injection should not be mixed or diluted with other solutions or drugs. It should not be added to intravenous fluids.

Presentation
Box of five ampoules of 2 ml