ASSIVAL®

INJECTION

Composition

Active Ingredient
Each ampoule of 2 ml contains:
Diazepam 10 mg

Other Ingredients
Propylene glycol, alcohol, sodium benzoate, benzyl alcohol, benzoic acid, water for injection.

Action
Diazepam is a benzodiazepine derivative which possesses anxiolytic, anticonvulsant and muscle relaxant properties.
Assival acts on parts of the limbic system, the thalamus and hypothalamus, and induces calming effects.
Major muscle relaxant actions may be due to enhancement of presynaptic inhibition in the central nervous system, as well as to a direct peripheral action on the contractile process of the muscle. Action at the neuromuscular synapse may involve direct muscle depression.

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, Assival may be useful in the symptomatic relief of tremor, impending or acute delirium tremens and hallucinosis.
Assival is a useful adjunct in the relief of skeletal muscle spasm, spasticity, stiff-man syndrome and tetanus.
When used intravenously, Assival Injection is a useful adjunct in status epilepticus and severe recurrent convulsive seizures.
As premedication in patients undergoing surgical procedures (the intra-muscular route is preferred) or in patients undergoing cardioversion (when the intravenous route is preferred).

Contraindications
Known hypersensitivity to benzodiazepines or to any other ingredient of the preparation.
First trimester of pregnancy and in breastfeeding.
Acute pulmonary insufficiency.
Severe hepatic insufficiency.
Respiratory depression.
Psychoses.
Acute narrow-angle glaucoma (benzodiazepines may be used in patients with open-angle glaucoma who are receiving appropriate therapy).
Myasthenia gravis.
Sleep apnea syndrome.
Assival Injection should not be administered to patients in shock, coma or in acute alcoholic intoxication with depression of vital signs.

**Warnings**

**After administration of the injection, ambulation should be delayed until complete alertness is restored.**

Parenteral (I.M. or I.V.) therapy is indicated primarily in acute states.

When used intravenously, Assival should be injected slowly, taking at least 1 minute for each 5 mg (1 ml) given, and 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.

Assival should not be injected intra-arterially as this may produce arteriospasm resulting in gangrene which may require amputation.

Assival should be administered parenterally with extreme care (particularly IV) 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.

Since lingual obstruction of the airway may occur, particularly in children and in the elderly, caution is required to maintain a free airway in patients receiving the injection.

Rapid injection or the use of veins with too small a lumen carries the risk of thrombophlebitis. IV injection should therefore be given directly into a large lumen vessel, such as an antecubital vein, and the drug should be administered slowly, at the rate of no more than 5 mg (1 ml/min). Extreme care should be taken to avoid intra-arterial administration or extravasation.

Concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea. When diazepam is used in patients taking narcotic analgesics, the dosage of the narcotic should be reduced by at least one-third and administered in small increments. In some instances, the use of a narcotic may not be necessary. Diazepam injection should not be administered to patients with acute alcoholic intoxication with depression of vital signs.

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 anesthetics 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 readminister the drug. However, Assival 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.

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, decrease dosage gradually to avoid the possibility of withdrawal symptoms.
Use in Pregnancy
Benzodiazepines have the potential to cause fetal harm when administered to pregnant women. If this drug is used during pregnancy or the patient becomes pregnant while taking this drug, she should be informed of the potential hazard to the fetus.

Benzodiazepines are assumed to be capable of causing an increased risk of congenital abnormalities when administered to pregnant women during the first trimester. Therefore, their use during this period should almost always be avoided (see Contraindications).

The possibility that women of child-bearing potential may be pregnant when therapy is instituted should be considered.

Use in Breastfeeding
Benzodiazepines are excreted in breast milk. Since neonates metabolize this drug more slowly than adults, and accumulation of the drug and its metabolites to toxic levels is possible, it should not be administered to nursing women (see Contraindications).

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 has been attributed to maternal ingestion of benzodiazepines as well as neonatal flaccidity and respiratory problems. 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.

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

Use in Pediatrics
In order to obtain maximal clinical effect with the minimum amount of drug, and thus to 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 three-minute period in a dosage not to exceed 0.25 mg/kg. 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.

Use in the Elderly
Elderly and debilitated patients and those with organic brain disorders have been found to be very prone to CNS depression following even low doses of diazepam. Diazepam injection should be used in those patients with caution and in low doses to preclude development of ataxia, sedation and other possible adverse effects.

Use in Hepatic Insufficiency
Decreases in clearance and protein binding, and increases in volume of distribution and half-life has 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.
**Use in Patients with Renal Insufficiency** (see Precautions)

Since metabolites of diazepam are excreted by the kidney, in order to avoid their excess accumulation, caution should be exercised in the administration of the drug to patients with compromised kidney function.

**Use before Bronchoscopy and Laryngoscopy**

Since there are insufficient data available to establish the safety of diazepam injection prior to bronchoscopy and laryngoscopy, its use is not recommended.

**Use before Gastroscopy, Esophagoscopy, Cardioversion and Surgical Procedures:**

Diazepam injection should be used only under conditions in which safeguards are available should laryngospasm and circulatory or respiratory depression occur.

**Adverse Reactions**

Adverse reactions with different benzodiazepines vary in type and frequency. Some are dose-related, while others involve individual patient sensitivity. Although not all of the following adverse reactions have been attributed specifically to each benzodiazepine drug, the potential for their occurrence exists. This should be borne in mind when drugs of this class are administered.

Side effects most commonly reported have been drowsiness, fatigue, muscle weakness and ataxia, especially in elderly or debilitated patients.

Infrequently reported side effects are as follows:

**Central Nervous System**

- Sedation and sleepiness, depression, hypoactivity, lightheadedness, restlessness, confusion, delirium, headache, slurred speech, dysarthria, syncope, vertigo, dizziness, vivid dreams, psychomotor retardation.

  Occasionally, prolonged use with this medicine may cause behavioral changes and paranoid symptoms.

**Gastrointestinal**

- Constipation, diarrhea, dry mouth, nausea, vomiting, increased salivation.

**Genitourinary**

- Incontinence, enuresis, changes in libido, urinary retention, menstrual irregularities.

**Cardiovascular**

- Bradycardia, tachycardia, hypotension, palpitations.

**Ophthalmological**

- Visual disturbances, diplopia.

**Dermatological**

- Urticaria, pruritus, skin rash, dermatitis.

**Laboratories Data**

Elevated transaminases and alkaline phosphatase

**Other**

Hepatic dysfunction (including hepatitis and jaundice), blood dyscrasias, including agranulocytosis, anemia, thrombocytopenia, eosinophilia.

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

Minor changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during and after diazepam therapy and are of no known significance.
Venous thrombosis and phlebitis may be encountered at the site of injection.

**Precautions**

Although hypotension has rarely occurred, administer 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. Metabolites of diazepam are excreted by the kidney; to avoid their excess accumulation, caution should be exercised in the administration to patients with compromised kidney function.

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 readminister 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.

If use in patients with seizure disorders results in an increase in the frequency or severity of grand mal seizures, there may be a need to increase the dosage of standard anticonvulsant medication.

**Drug Interactions**

**Diazepam/ Cimetidine/ Oral Contraceptives/ Disulfiram/ Fluoxetine/ Isoniazide/ Ketoconazole/ Metoprolol/ Propoxyphene/ Propranolol/ Valproic Acid:** The elimination of diazepam that undergoes oxidative hepatic metabolism may be decreased by these drugs due to inhibition of hepatic metabolism. The pharmacological effects of diazepam may be increased and excessive sedation/impaired psychomotor function may occur.

**Diazepam/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 (see above), ketoconazole, fluvoxamine, fluoxetine, and omeprazole.

**Diazepam/Phenytoin:** There have been reports that the metabolic elimination of phenytoin is decreased by diazepam.

**Diazepam/Erythromycin:** Concurrent administration of erythromycin with diazepam, which is metabolized by oxidation, may result in inhibition of metabolism of the benzodiazepine leading to delayed elimination and increased plasma concentrations of the benzodiazepine. Dosage reduction of diazepam may be required in some patients.

**Diazepam/Rifampin:** Concurrent administration may enhance the elimination of diazepam, resulting in decreased plasma concentrations; dosage adjustment of diazepam may be necessary. Data as to whether this effect applies to other benzodiazepines are not available.

**Diazepam/Isoniazid:** Concurrent use may enhance the elimination of diazepam, resulting in decreased plasma concentrations; dosage adjustment of the diazepam may be necessary. Data as to whether this effect applies to other benzodiazepines are not available.

**Diazepam/Lithium Carbonate:** In one patient, concurrent administration of diazepam and lithium carbonate reportedly resulted in hypothermia.

**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 neuro-psychiatric symptoms and cardiac arrhythmias may occur. Digoxin serum levels should be monitored.

**Diazepam/ Levodopa:** Coadministration 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.

Benzodiazepines/Centrally-Acting Drugs/Alcohol: Benzodiazepines may have a potentiating effect on centrally-acting drugs such as neuroleptics, tranquilizers, antidepressants, hypnotics, antiepileptics, analgesics, and anesthetics. When these drugs are administered concomitantly with benzodiazepines, their dosage should be reduced.

Benzodiazepines may also intensify the response to alcohol. Patients should be advised to avoid drinking alcoholic beverages while under treatment with this drug.

Benzodiazepines/Levodopa: Rare reports indicate that patients treated with levodopa experienced diminished control of parkinsonian symptoms when chlordiazepoxide or diazepam was added to their therapeutic regimen. For this reason, benzodiazepines should be administered with caution to patients receiving levodopa.

Benzodiazepines/Ergot Alkaloids: Although specific drug interaction studies are not available, concomitant use of ergotamine with some benzodiazepines (e.g., alprazolam, triazolam) may result in decreased metabolism of the benzodiazepine; caution is therefore advised.

Benzodiazepines/Ranitidine: There have been reports of increased systemic availability of benzodiazepines (e.g., oral midazolam, triazolam) when these benzodiazepines were administered concomitantly with ranitidine. The mechanism has not been fully elucidated.

Benzodiazepines/Smoking: Cigarette smoking may decrease the sedative effects of usual doses of benzodiazepines. Clearance of benzodiazepines may be increased in smokers compared with nonsmokers. Plasma alprazolam concentrations reportedly are decreased by up to 50% in cigarette smokers compared with non-smokers.

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, maximum 5 mg (1 ml) per minute; 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 Assival directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.

When Assival is administered intramuscularly, it should be injected deeply into the muscle.

Once the acute symptomatology has been controlled with injectable Assival, the patient may be placed on oral therapy with Assival 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 to 4 hours, if necessary.

**Acute Alcohol Withdrawal**

Initially, 10 mg I.M. or I.V., then 5-10 mg after 3 to 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. Generally 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**

5-10 mg I.M. or I.V. initially, 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 route), before surgery.

**Cardioversion**

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

**Children**

*Note: Since the diluting solution for Assival 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. 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, 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 to 4 hours, may be required to control tetanus spasms. Respiratory assistance should be available.
Status Epilepticus and Severe Recurrent Convulsive Seizures
Infants over 30 days of age and children under 5 years, 0.2-0.5 mg, slowly, every 2-5 minutes, up to a maximum of 5 mg (I.V. preferred). Children 5 years or older, 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.

Overdosage

Manifestations
Somnolence, confusion, coma, and diminished reflexes. Respiratory depression and hypotension have been minimal following overdosage.

Treatment
General supportive measures should be employed along with intravenous fluids. An adequate airway should be maintained. Hypotension may be combated by the administration of noradrenaline or metaraminol.
Dialysis is of limited value.
Flumazenil injection (Anexate), a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines, and may be used in situations when an overdose with a benzodiazepine is known or suspected.
Prior to the administration of flumazenil, the complete package insert of the product should be consulted, and necessary measures should be instituted to secure airway, ventilation, and intravenous access.
Flumazenil is intended as an adjunct to, not a substitute for, proper management of benzodiazepine overdose.
Patients treated with flumazenil should be monitored for resedation, respiratory depression, and other residual benzodiazepine effects, for an appropriate period after treatment. Awareness is required regarding a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.

Pharmaceutical Precautions
Do not mix or dilute Assival Injection with other solutions or drugs. Do not add to intravenous fluids.

Storage
Store below 25°C.
Protect from light.

Product Registration No.: 027 24 21645 21

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