PRODUCT MONOGRAPH

DIAZEPAM INJECTION SDZ

Diazepam Injection BP

Solution for Injection, 5 mg/mL
Preservative Free

Anxiolytic–Sedative

Sandoz Canada Inc.
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Boucherville, QC, Canada
J4B 7K8

Date of Revision: May 11, 2012

Control No: 154076

DIAZEPAM INJECTION SDZ
5 mg/mL

THERAPEUTIC CLASSIFICATION

Anxiolytic - Sedative

ACTIONS AND CLINICAL PHARMACOLOGY

Diazepam is an anxiolytic-sedative drug useful in the symptomatic relief of anxiety and tension states associated with psychoneurotic disorders. It also has anticonvulsant properties and adjunctive value in the relief of certain neurospastic conditions. As an anticonvulsant, diazepam injectable has a major use in the control of status epilepticus.

Peak blood levels are reached very rapidly after intravenous administration of diazepam as compared to one hour after a single oral dosing and are of the same magnitude. The acute half-life is 2-3 hours with a slower decline thereafter, possibly due to tissue storage. Repeated doses further increase blood levels. In humans, comparable blood levels of diazepam were obtained in maternal and cord blood indicating rapid placental transfer of the drug following parenteral administration.

INDICATIONS AND CLINICAL USE

Diazepam Injection SDZ is indicated when a rapid response to the use of diazepam is desired and may be useful:

- To control prolonged seizure activity (status epilepticus) not associated with acute neurologic disorders.
- To alleviate the symptoms of acute alcoholic withdrawal, including delirium tremens.
- In acute anxiety or tension states related to non-psychotic emotional disorders and to relieve spasticity in cerebral palsy, athetosis and the rare "Stiff Man Syndrome".

CONTRAINDICATIONS

Diazepam Injection SDZ is contraindicated in myasthenia gravis, acute narrow angle glaucoma, and known hypersensitivity to benzodiazepines. It is also contraindicated in infants.

WARNINGS AND PRECAUTIONS

Diazepam Injection SDZ should not be administered to patients in shock or coma and should not be added to parenteral fluids. Neither should it be further diluted or mixed with other drugs. Rare reports of apnea or cardiac arrest have been noted, usually following IV (intravenous) administration, especially in elderly or very ill patients and those with limited pulmonary reserve. Duration is generally brief. 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 Diazepam Injection SDZ.

Rapid injection or the use of veins with too small a lumen carries the risk of thrombophlebitis. Intravenous injection should be directly into a large lumen vessel, such as an antecubital vein, and the ampoule solution should be administered slowly, e.g. 1 mL (5 mg) per minute. Do not mix or dilute Diazepam Injection SDZ with other solutions or drugs.

Intra-arterial injection must be carefully avoided on account of the danger of necrosis.

Use in the Elderly: Elderly and debilitated patients and those with organic brain disorders have been found to be very prone to central nervous system depression following even low doses of diazepam. For these patients, Diazepam Injection SDZ should be used with caution and in low doses to preclude development of ataxia, sedation or other possible adverse effects.

Use in Emotional Disorders: Diazepam Injection SDZ is not recommended in the treatment of psychotic or severely depressed patients. Precautions are indicated for severely depressed patients or those who show any evidence of impending depression, particularly the recognition that suicidal tendencies may be present and protective measures may be necessary.

Since excitement and other paradoxical reactions may result from use of the drug in psychotic patients, it should not be used in ambulatory patients suspected of having psychotic tendencies.

Use in Status Epilepticus: Diazepam Injection SDZ is not recommended as a substitute for standard anticonvulsant medication in the long-term control of epilepsy. Appropriate anticonvulsant therapy should be instituted or continued when necessary, as soon as possible after interruption of the status epilepticus. Although diazepam injectable is used to control status epilepticus, it may occasionally induce or aggravate seizures in some patients with convulsive disorders.

Use in Pregnancy: Diazepam Injection SDZ should not be used during the first trimester of pregnancy except if absolutely necessary. The safety and efficacy of diazepam injectable in obstetrics have not yet been established.

Use in Children: The safety and efficacy of diazepam injectable have not been established in children under 12.

Potentiation of Drug Effects: Careful consideration should be given if Diazepam Injection SDZ is to be combined with other psychotropic agents (phenothiazines, barbiturates, MAO inhibitors and other antidepressants) because the pharmacological action of these agents might potentiate the action of diazepam injectable.

Patients should be advised to abstain from alcohol during treatment with Diazepam Injection SDZ

In view of possible adverse reactions and potentiation of effects, patients should be advised to abstain from CNS depressant drugs during treatment with Diazepam Injection SDZ.

Drug Dependence: Abrupt cessation of large doses of diazepam after prolonged periods may precipitate acute withdrawal symptoms and, in these cases, the drug should be discontinued gradually. Caution should be exercised when it is considered necessary to administer Diazepam Injection SDZ to addiction-prone individuals.

Interference with Serum Creatine Phosphokinase Determinations: As with a number of other intramuscular dosage forms, intramuscular administration of diazepam injectable (but not oral or intravenous administration) can lead to a rise in serum creatine phosphokinase activity. A maximum level is usually noticed between 12 and 24 hours after intramuscular injection. These elevated readings should be taken into account in the event of differential diagnosis of myocardial infarction.

General: After parenteral administration of Diazepam Injection SDZ, ambulation should be delayed at least one or two hours or until complete alertness is restored.

Patients receiving Diazepam Injection SDZ should be advised to proceed cautiously wherever mental alertness and physical coordination are required.

The usual precautions in treating patients with impaired renal and hepatic functions should be observed. If Diazepam Injection SDZ is administered for protracted periods, periodic blood counts and liver function tests may be advisable.

Diazepam Injection SDZ should not be administered to patients in shock or coma and should not be added to parenteral fluids. Neither should it be further diluted or mixed with other drugs.

ADVERSE REACTIONS

The most common adverse reactions reported for diazepam injection are drowsiness and ataxia.

Other reactions noted less frequently are fatigue, dizziness, nausea, blurred vision, diplopia, vertigo, headache, slurred speech, tremors, hypoactivity, dysarthria, euphoria, impairment of memory, confusion, depression, incontinence or urinary retention, constipation, skin rash, generalized exfoliative dermatitis, hypotension, tachycardia, flushing, hematuria, changes in libido, pain at the site of injection and phlebitis following intravenous administration.

The more serious adverse reactions occasionally reported are leucopenia, jaundice, hypersensitivity and paradoxical reactions. Circulatory and respiratory depression may follow rapid intravenous administration of diazepam injection.

Paradoxical reactions such as hyperexcited states, anxiety, excitement, hallucinations, increased muscle spasticity, insomnia, rage, as well as sleep disturbances and stimulation have been reported,

should these occur, the drug should be discontinued.

Minor changes in EEG patterns have been observed in patients on diazepam injection therapy. These changes consist of low to moderate voltage fast activity, 20-30 cycles per second, and are of no known significance.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to:** **Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

OVERDOSAGE

The main symptoms of overdosage are drowsiness, oversedation and ataxia. When the effects of the drug overdosage begin to wear off, the patient exhibits some jitteriness and overstimulation. The cardinal manifestations of overdosage are drowsiness and confusion, reduced reflexes and coma. There are minimum effects on respiration, pulse and blood pressure unless the overdosage is extreme.

There is no specific antidote known. If necessary, a CNS stimulant such as caffeine or methylphenidate may be administered with caution. Supportive measures should be instituted as indicated: maintenance of an adequate airway, levarterenol bitartrate or metaraminol for hypotension. Dialysis appears to be of little value.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

Diazepam Injection SDZ is used without diluent for both the IM (intramuscular) and the IV routes. The intramuscular route should be preferred whenever the indication and urgency of the clinical situation permit.

While the dosage should be individualized for maximum beneficial effect, as a general rule the mean dose for both the IV and IM routes is:

	USUAL DOSAGE
1. Status epilepticus including severe recurrent seizures: For the control of prolonged seizure activity.	5 to 10 mg IV (preferred route) or IM initially. Repeat in 2 to 4 hours, if necessary.
2. Acute alcoholic withdrawal: To alleviate the symptoms of acute alcoholic withdrawal including delirium tremens.	10 mg IM or IV initially, then 5 mg to 10 mg in 3 to 4 hours, if necessary.
3. Acute anxiety related to stressful conditions or non-psychotic emotional disorders.	2 mg to 10 mg IM or IV. Repeat in 3 to 4 hours, if necessary.
4. For the relief of muscle spasm in cerebral palsy athetosis, the rare "Stiff Man Syndrome" and adjunctively in tetanus.	5 mg to 10 mg IM or IV initially, then 5 mg to 10 mg in 3 to 4 hours, if necessary. For tetanus, larger doses may be required.
Elderly and debilitated patients: (See WARNINGS and PRECAUTIONS)	2 mg to 5 mg IM or IV

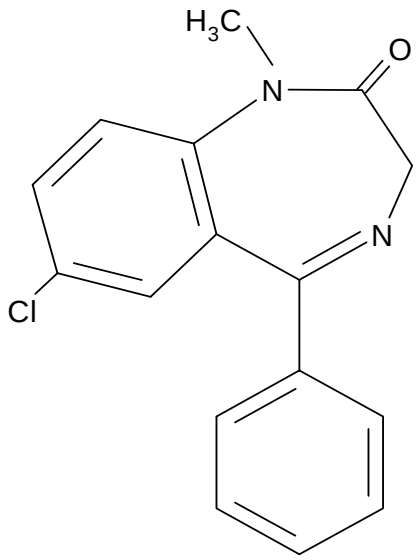
Intramuscular: Diazepam Injection SDZ should be injected deeply into the muscle.

Intravenous: Diazepam Injection SDZ should be administered slowly, i.e. 5 mg (1 mL) per minute.

In acute conditions, the injection may be repeated within one hour although an interval of three to four hours is usually satisfactory. Generally not more than 30 mg should be given in an eight-hour period.

PHARMACEUTICAL INFORMATION

Diazepam is 7-chloro-1, 3-dihydro-1-methyl-5-phenyl-2H-1, 4-benzodiazepin-2-one, and has the following structural formula:



Diazepam

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each mL contains diazepam 5 mg, propylene glycol 550 mg, ethanol 96% 250 mg, sodium hydroxide to adjust pH and water for injection. Preservative free.

Diazepam Injection SDZ 5 mg/mL is available in 2 mL ampoules, boxes of 10.

Store between 15 and 30 °C. Protect from light.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitation, discolouration and leakage prior to administration whenever solution and container permit.

DETAILED PHARMACOLOGY

Diazepam is a benzodiazepine with CNS depressant properties and a somewhat flatter dose-response slope than the sedative-hypnotic drugs. In laboratory animals it produces, in varying doses, taming, disinhibitory, sedative, anticonvulsant, muscle relaxant, ataxic hypnotic effects.

As with the sedative-hypnotic drugs, at doses producing only mild sedation, it reduces slightly the

behavioural arousal, increases responsiveness to environmental stimuli, suppresses passive avoidance behaviour and increases approach behaviour, while, at slightly higher doses, it appears to increase errors of commission in performing tasks and may produce drowsiness, muscle weakness and ataxia. The most selective behavioural properties observed in laboratory animals at low doses are suppression of passive avoidance behaviour and "trace" avoidance conditioning, blocking the extinction of active avoidance behaviour and increased food intake.

Diazepam selectively suppresses subcutaneous metrazol-induced convulsions, but is less effective against maximal electroshock convulsions and relatively ineffective against minimal electroshock convulsions. It reduces body tone in the cat at sub-ataxic doses and is active in the inclined screen test, and in blocking decerebrate rigidity and the spinal reflex in the cat at higher doses.

Parenteral administration decreases the amplitude of local evoked potentials recorded from the mesencephalic reticular formation, septal region, amygdaloid complex and hyppocampus in the cat and monkey. It also depresses the cardiovascular and intestinal responses to stimulation of the hypothalamus in the cat.

Diazepam is relatively devoid of autonomic effects and does not significantly reduce locomotor activity at low doses, or depress amphetamine-induced excitation. In high doses it activates the drug metabolizing enzymes in the liver. Diazepam also possesses dependence liability and may produce withdrawal symptoms, but has a wide margin of safety against poisoning.

Metabolism studies in animals and man have indicated that oral diazepam is rapidly absorbed from the gastrointestinal tract. Peak blood levels are reached within 1 to 2 hours after administration. The acute half-life is 6 to 8 hours with a slower decline thereafter, possibly due to tissue storage.

With the parenteral form, peak blood levels are reached within 15 minutes after intravenous administration and are of the same magnitude as after oral administration. The respective half-life is approximately 2 to 3 hours.

The distribution and fate of tritium-labelled diazepam in man has indicated that the drug has a rapid and extensive uptake by tissues. Although the radioactivity in blood appears to represent mainly the intact drug, diazepam was shown to be excreted exclusively in the form of its metabolites. The two major metabolites are oxazepam glucuronide and N-demethylated diazepam.

TOXICOLOGY

Acute Toxicity

Administration Route	**LD_{50} (mg/kg)**	
	Mouse	**Rat**
Intravenous	24.9	51.8
Intramuscular	66.0	> 50

Administration Route	LD_{50} (mg/kg)	
	Mouse	**Rat**
Oral	1050	1050

Subacute Toxicity
Diazepam has been administered orally at 20, 80 and 320 mg/kg to male and female rats, for a 12-week period.

Hematological and biochemical evaluations as well as urinalyses have been performed after 5 and 12 weeks of treatment respectively.

Following 12 weeks of treatment, the animals were sacrificed and their tissues submitted to histopathological examination. These toxicity studies on diazepam gave results similar to those obtained with other diazepam preparations.

An increase in the size of the liver as well as hepatic degeneration have been observed following benzodiazepine administration.

Local Irritation
Diazepam 0.1 mL was administered to rabbits twice daily for five consecutive days. The injections were made in the marginal vein or one ear, the other ear being used as control. Local reactions such as temperature elevation, edema and erythema were observed, but these manifestations were transient and disappeared completely within 7 days of the last injection of diazepam.

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