PRODUCT MONOGRAPH

DIAZEMULS*

(diazepam injectable emulsion)

5 mg/mL

Anxiolytic-sedative

Actavis Group PTC ehf
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Pfizer Canada Inc., Licensee

PRODUCT MONOGRAPH

NAME OF DRUG

DIAZEMULS*

(diazepam injectable emulsion)

THERAPEUTIC CLASSIFICATION

Anxiolytic-sedative

ACTION AND CLINICAL PHARMACOLOGY

DIAZEMULS is an injectable emulsion of diazepam, a drug with known anxiolytic-sedative and muscle relaxant properties. Diazepam has been found useful for short-term symptomatic relief of excessive anxiety and tension in patients with anxiety neurosis, although anxiety and tension associated with the stresses of everyday life usually do not require treatment with anxiolytic drugs.

Diazepam must first be released from the oil phase of the DIAZEMULS emulsion before it can exert a therapeutic effect. In fact, peak blood levels of diazepam are reached only after 15 minutes following intravenous injection of DIAZEMULS, and after 2 hours following intramuscular administration. Subsequent to a rapid distribution phase, diazepam undergoes a longer elimination phase, which varies with age, from approximately 20 hours at age 20 to approximately 80 hours at age 80.

Diazepam is metabolized in the liver to N-desmethyl-diazepam, and to some extent to N-methyl-oxazepam, which in turn is metabolized to oxazepam. Although these metabolites are pharmacologically active, only N-desmethy l-diazepam is formed in sufficient quantity to

produce significant clinical effects. The desmethyl metabolite has an elimination half-life of 50 to 120 hours.

Diazepam and its metabolites are excreted mainly in the urine, as glucoronides or sulfates.

Diazepam crosses the placenta and is secreted in breast milk. It is approximately 98% bound to plasma proteins.

INDICATIONS

DIAZEMULS (diazepam injectable emulsion) is indicated when an injectable preparation of diazepam is required. It has been found useful:

a) to alleviate the symptoms of acute alcohol withdrawal, such as acute agitation, tremor, impending or acute delirium tremens and hallucinosis;
b) as an adjunct prior to endoscopic procedures if apprehension, anxiety or acute stress reactions are present, and to diminish the patients recall of the procedures (see *WARNINGS*);
c) for the relief of muscle spasm in cerebral palsy, athetosis and stiff man syndrome;
d) as premedication for relief of anxiety states prior to surgical procedures (i.m. route) or cardioversion (i.v. route).

CONTRAINDICATIONS

DIAZEMULS (diazepam injectable emulsion) is contraindicated in patients with known hypersensitivity to diazepam or to the components of the emulsion vehicle (see section *FORMULATION AND AVAILABILITY*); myasthenia gravis; acute narrow angle glaucoma, and open angle glaucoma unless patients are receiving appropriate therapy.

WARNINGS

DIAZEMULS (DIAZEPAM INJECTABLE EMULSION) SHOULD NOT BE ADMINISTERED TO PATIENT IN SHOCK OR COMA. THERE HAVE BEEN RARE REPORTS OF APNEA OR CARDIAC ARREST, USUALLY FOLLOWING I.V. ADMINISTRATION, ESPECIALLY IN ELDERLY OR VERY ILL PATIENTS AND IN THOSE WITH LIMITED PULMONARY RESERVE. RESUSCITATIVE EQUIPMENT INCLUDING THAT NECESSARY TO SUPPORT RESPIRATION SHOULD THEREFORE BE READILY 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 DIAZEMULS INJECTION.

RAPID INJECTION OR THE USE OF VEINS WITH TOO SMALL A LUMEN CARRIES THE RISK OF THROMBOPHLEBITIS. INTRAVENOUS INJECTION SHOULD THEREFORE BE DIRECTLY INTO A LARGE LUMEN VESSEL, SUCH AS AN ANTECUBITAL VEIN, AND THE DRUG SHOULD BE ADMINISTERED SLOWLY, AT THE RATE OF NO MORE THAT 5 MG (1 ML) PER MINUTE. EXTREME CARE SHOULD BE TAKEN TO AVOID INTRA-ARTERIAL ADMINISTRATION OR EXTRAVASATION.

WHEN USED INTRAVENOUSLY, DIAZEMULS SHOULD BE INJECTED DIRECTLY INTO THE VEIN WITHOUT PRIOR DILUTION OR MIXING WITH OTHER PRODUCTS OR SOLUTIONS (SEE *DOSAGE AND ADMINISTRATION*).

Concomitant use of barbiturates, alcohol or other central nervous system depressants increases depression with increased risk of apnea. When diazepam is used in a patient 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. DIAZEMULS should not be administered to patients with acute alcoholic intoxication with depression of vital signs.

Patients receiving DIAZEMULS should be cautioned against engaging in hazardous occupations requiring complete mental alertness, such as operating machinery and driving a motor vehicle.

Physical and Psychological Dependence

Withdrawal symptoms similar to those noted with barbiturates and alcohol may occur following abrupt discontinuance of diazepam (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Severe symptoms are usually limited to those patients who have received excessive doses over an extended period of time. Milder withdrawal symptoms have been reported more frequently following abrupt discontinuance of benzodiazepines. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and gradual tapering in dosage followed. Particularly addiction-prone individuals (such as drug addicts or alcoholics) should be under careful surveillance when receiving diazepam or other psychotropic agents because of the predisposition of such patients to habituation and dependence.

Use in Pregnancy

An increased risk of congenital malformations associated with the use of anxiolytic-sedative drugs including diazepam, meprobamate and chlordiazepoxide during the first trimester of pregnancy has been suggested in several studies. Therefore, the use of these drugs during pregnancy should almost always be avoided, unless the expected benefits are considered to outweigh the potential risks. The possibility that a woman of child-bearing potential may be pregnant at the time of institution of therapy should be considered.

Use in Obstetrics

The safety and efficacy of DIAZEMULS in obstetrics have not yet been established.

Use in Children

Efficacy and safety of diazepam have not been established in the neonate (30 days or less of age). Prolonged central nervous system depression has been observed in the neonate, apparently due to inability to biotransform diazepam into inactive metabolites.

In pediatric use, 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 to 30 minutes the initial dosage can be cautiously repeated. If, however, relief of symptoms is not obtained after a third administration, adjunctive therapy appropriate to the condition being treated should be considered.

PRECAUTIONS

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. DIAZEMULS (diazepam injectable emulsion) 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 Emotional Disorders

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

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

Use before Bronchoscopy and Laryngoscopy

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

Use before Gastroscopy, Esophagoscopy, Cardioversion and Surgical Procedures

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

Since an increase in cough reflex and laryngospasm may occur with peroral endoscopic procedures, the use of a topical anesthetic agent and the availability of necessary counter measures are recommended.

Concurrent use of narcotics and barbiturates with DIAZEMULS may produce a potentiation of effect and, when such combinations are used, appropriate reduction of dosage is required.

Use in Impaired Renal and Hepatic Function

The usual precautions in treating patients with impaired hepatic function should be observed. 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.

Potentiation of Drug Effects

Careful consideration should be given if diazepam is to be used concommitantly with other psychotropic agents such as phenothiazines, barbiturates, MAO inhibitors and other antidepressants, since the pharmacological action of these agents may potentiate the action of diazepam.

Due to the possible potentiation of effects and the occurrence of adverse reactions, patients should be advised to abstain from CNS depressant drugs during treatment with diazepam.

The clearance of diazepam and of certain other benzodiazepines can be delayed when used in association with Tagamet© (cimetidine).

Parenteral diazepam has produced hypotension or muscular weakness in some patients, particularly when used with barbiturates, narcotics and alcohol.

GENERAL

AFTER ADMINISTRATION OF DIAZEMULS, AMBULATION SHOULD BE DELAYED UNTIL COMPLETE ALERTNESS IS RESTORED.

ADVERSE REACTIONS

Evidence suggests that there is a lower incidence of local reactions when DIAZEMULS (diazepam injectable emulsion) is used. Side effects most commonly reported are drowsiness, fatigue and ataxia. Other adverse reactions less frequently reported include:

Central Nervous System: confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo and floppy infant syndrome.

Gastrointestinal:	constipation, nausea.
Urogenital:	incontinence, changes in libido, urinary retention.
Cardiovascular:	bradycardia, cardiovascular collapse, hypotension, venous thrombosis and phlebitis at site of injection.
Ophthalmological:	blurred vision, diplopia, nystagmus.
Dermatological:	urticaria, skin rash.
Other:	hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued. Minor changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during and after DIAZEMULS therapy and are of no known significance.

In peroral endoscopic procedures, coughing, depressed respiration, dyspnea, hyperventilation, laryngospasm and pain in throat or chest have been reported.

Because of isolated reports of neutropenia and jaundice, periodic blood counts and liver function tests are advisable during long-term therapy.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Manifestations of diazepam overdosage include somnolence, confusion, coma, and diminished reflexes. Respiration, pulse and blood pressure should be monitored, as in all cases of drug overdosage, although, in general, these effects have been minimal unless overdose is extreme. General supportive measures should be employed, along with intravenous fluids, and an adequate airway maintained. Hypotension may be combatted by the use of Levophed© (levarterenol). Dialysis is of limited value.

DOSAGE AND ADMINISTRATION

Dosage should be individualized for maximal beneficial effect. The usual recommended dose in older children and adults ranges from 2 mg to 20 mg i.m. or i.v., depending on the indication and/or the severity of the condition (see *DOSAGE* subsection for specific indications). In acute conditions the injection may be repeated within one hour, although an interval of 3 to 4 hours is usually satisfactory.

When a continuing drug effect is required, lower doses (usually 2 mg to 5 mg) with small increments if necessary, should be used in elderly or debilitated patients and when other sedative drugs are administered. (See *WARNINGS* and *ADVERSE REACTIONS).*

For dosage in pediatric use, see *DOSAGE* subsection and *WARNINGS*.

Because of its delayed action, DIAZEMULS (diazepam injectable emulsion) is not recommended for the management of status epilepticus.

Intravenous Use

DIAZEMULS should be injected slowly, taking at least one minute for each 5 mg (1 mL) administered. Extreme care should be taken to avoid intra-arterial administration or extravasation (See *WARNINGS*, particularly for use in children).

WHEN INTRAVENOUS USE IS INDICATED, FACILITIES FOR RESPIRATORY ASSISTANCE SHOULD BE READILY AVAILABLE.

WHEN USED INTRAVENOUSLY, DIAZEMULS SHOULD BE INJECTED DIRECTLY INTO THE VEIN WITHOUT PRIOR DILUTION OR MIXING WITH OTHER PRODUCTS OR SOLUTIONS. DIAZEMULS may, however, be mixed or diluted with Intralipid, but such an admixture should be used within 6 hours. If it is not feasible to administer DIAZEMULS directly i.v., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.

DIAZEMULS has been shown to be incompatible with morphine and glycopyrrolate. Mixing or further diluting DIAZEMULS with products or solutions other than its own emulsion base (Intralipid) may de-stabilize the emulsion. Although such an effect may not be recognizable on visual inspection, it could give rise to potentially serious adverse reactions. Polyethylene-lined or glass infusion sets and polyethylene / polypropylene plastic syringes are recommended for use with DIAZEMULS. Do not use infusion sets containing polyvinyl-chloride.

Intramuscular Use

DIAZEMULS should be injected deeply into the muscle.

DOSAGE

Adults	**Usual Dosage**
Acute anxiety or tension states related to stressful conditions or non-psychotic emotional disorders when parenteral administration is required.	Depending on severity, 2 to 10 mg, i.m. or i.v. Repeat in 3 to 4 hours, if necessary.
Acute alcohol withdrawal: As an aid in symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis.	Initially 10 mg i.m. or i.v., then 5 to 10 mg in 3 to 4 hours, if necessary.
Minor surgical procedures including esophagoscopy and gastroscopy: as an adjunct in relieving anxiety states that may be present before these procedures.	Approximately 5 to 10 mg, i.m. or i.v., as required, about 30 minutes prior to procedures.
For the relief of muscle spasm in cerebral palsy, athetosis and stiff man syndrome.	Initially, 5 to 10 mg i.m. or i.v., then 5 to 10 mg in 3 to 4 hours, if necessary.
Pre-operative medication for the relief of anxiety states. If pre-medications other than atropine sulfate, scopolamine hydrobromide, meperidine or fentanyl citrate are desired, they must be administered in separate syringes.	Extreme caution must be exercised in patients with chronic lung disease or unstable cardiovascular status. 10 mg i.m. or i.v. 1 to 2 hours before surgery.
Cardioversion: to relieve anxiety and tension and to reduce recall of procedure.	5 to 10 mg i.v., within 10 to 20 minutes prior to procedure.
Pediatric: See **WARNINGS**	Dosage not to exceed 0.25 mg/kg slowly over a 3-minute period.
Elderly and Debilitated: See **PRECAUTIONS**	2 to 5 mg, i.m. or i.v.

Once the acute symptomatology has been properly controlled with DIAZEMULS (diazepam injectable emulsion), the patient may be placed on oral therapy with diazepam if further treatment is required.

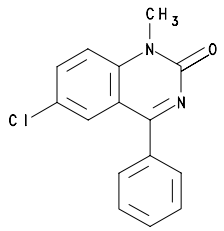
PHARMACEUTICAL INFORMATION

Drug substance

Proper name: Diazepam

Chemical name: 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1, 4-benzodiazepin-2-one

Structural formula:



Molecular formula: C_{16} H_{13} CL N_2O

Molecular weight: 284.74

Physical form: White or almost white crystalline powder

Solubility: Very slightly soluble in water, soluble in alcohol (95%), readily soluble in chloroform.

Melting point: 125-126°C

Composition

Each mL contains 5 mg of diazepam dissolved in the oil phase of an oil/water emulsion compounded with purified soybean oil 150 mg, acetylated monoglycerides 50 mg, purified egg

phospholipids 12 mg, glycerol anhydrous 22.0 mg and sodium hydroxide to adjust pH to approximately 8.

DIAZEMULS (diazepam injectable emulsion) is a sterile formulation and contains no preservatives. It is intended for intravenous or intramuscular use only.

Stability and Storage Recommendation

DIAZEMULS should be stored at 15 - 25°C.

Do not freeze.

AVAILABILITY

Packages of 10 x 2 mL ampoules.

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 and hynoptic effects.

As with the sedative-hypnotic drugs, at doses producing only mild sedation, it reduces slightly the behavioral arousal, increases responsiveness to environmental stimuli, suppresses passive avoidance behavior and increases approach behavior, 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 behavioral properties observed in laboratory animals at

low doses are suppression of passive avoidance behavior and "trace" avoidance conditioning, blocking the extinction of active avoidance behavior 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 subataxic 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 hippocampus 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.

Kinetics

The vehicle used in DIAZEMULS (diazepam injectable emulsion) is identical to one of the lipid preparations used in parenteral alimentation (Intralipid). The mean lipid particle diameter of DIAZEMULS is 0.18 μm as determined by means of a sedimentation technique. In the same study the mean lipid particle diameters of Intralipid 10% and 20% were 0.14 and 0.21 μm, respectively.

When compared with diazepam solutions containing propylene glycol, DIAZEMULS was completely bioavailable by the i.v. and i.m. routes based on relative AUC's and maximum plasma concentrations. However, the initial plasma concentrations of diazepam were lower for the emulsified preparation following both routes of administration.

TOXICOLOGY

Acute toxicity

The LD50 in mice is 283.3 mg/kg.

Subacute toxicity

In a five-week study, 6 male and 6 female rats received, intravenously, 0.5 mL/kg saline, DIAZEMULS (diazepam injectable emulsion) placebo (vehicle) and DIAZEMULS. This constitutes a 2.5 mg/kg dose of diazepam. There were no findings other than a slight ataxia following dosing.

In another five-week study, two dogs were given 0.1 mL/kg (0.5 mg/kg diazepam) of DIAZEMULS, intravenously. There were no pathological findings.

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