

Attachment 2

Proposed DiaJect Auto-injector Package Insert

C-IV

DiaJect™

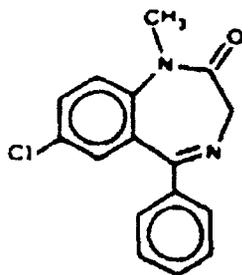
10 mg Diazepam Auto-Injector

DESCRIPTION

Diazepam injection is a sterile solution packaged within an injection device that delivers intramuscularly its entire 2 mL contents automatically upon activation. Each mL contains 5 mg diazepam compounded with 40% propylene glycol, 1.0% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

Diazepam is a benzodiazepine derivative. Chemically, diazepam is 7-chloro-1,3 dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. It is a colorless crystalline compound, insoluble in water and has a molecular weight of 284.74.

Structural formula:



CLINICAL PHARMACOLOGY

In animals, diazepam appears to act on parts of the limbic system, the thalamus and hypothalamus, and induces calming effects. Diazepam, unlike chlorpromazine and reserpine, has no demonstrable peripheral autonomic blocking action, nor does it produce extrapyramidal side effects. However, animals treated with diazepam do have a transient ataxia at higher doses. Diazepam was found to have transient cardiovascular depressor effects in dogs. Long-term experiments in rats revealed no disturbances of endocrine function. Injections into animals have produced localized irritation of tissue surrounding injection sites and some thickening of veins after intravenous use.

Pharmacokinetics (auto-injector): A study performed in 24 healthy male subjects comparing the I.M. Injection of 10 mg of diazepam in the mid-anterior/lateral thigh by the auto-injector versus 10 mg I.M. by a syringe (operated manually) indicates that the mean percent availability of the drug from the auto-injector is 100% of that obtained from the syringe.

In addition, the mean C_{max} value from the auto-injector was 314 ng/mL (c.v. = 18.7%, range 185 to 439 ng/mL) and 48.6 ng/mL (c.v. = 19.8%, range 29.4 to 69.7 ng/mL) for diazepam and desmethyldiazepam, respectively, while the syringe gave corresponding values of 287 ng/mL (c.v. = 18.9%, range 174 to 378 ng/mL) and 47.2 ng/mL (c.v. = 19.4%, range 33.1 to 61.2 ng/mL) for diazepam and desmethyldiazepam, respectively. The corresponding mean T_{max} values were 1.47 hours (c.v. = 69.9%, range 0.8 to 6 hours) and 61.0 hours (c.v. = 56.8%, range 24 to 144 hours) for diazepam and desmethyldiazepam for the auto-injector whereas the syringe gave values of 1.31 hours (c.v. = 32%, range 0.7 to 2.0 hours) and 54.5 hours (c.v. = 47.3%, range 12 to 96 hours) for diazepam and desmethyldiazepam, respectively.

ANIMAL PHARMACOLOGY

Oral LD 50 of diazepam is 720 mg/kg in mice and 1240 mg/kg in rats. Intraperitoneal administration of 400 mg/kg to a monkey resulted in death on the sixth day.

Reproduction Studies: A series of rat reproduction studies was performed with diazepam in oral doses of 1, 10, 80 and 100 mg/kg given for periods ranging from 60-228 days prior to mating. At 100 mg/kg there was a decrease in the number of pregnancies and surviving offspring in these rats. These effects may be attributable to prolonged sedative activity, resulting in lack of interest in mating and lessened maternal nursing and care of the young. Neonatal survival of rats at doses lower than 100 mg/kg was within normal limits. Several neonates, both controls and experimentals, in these rat reproduction studies showed skeletal or other defects. Further studies in rats at doses up to and including 80 mg/kg/day did not reveal significant teratological effects on the offspring. Rabbits were maintained on doses of 1, 2, 5 and 8 mg/kg from day 6 through day 18 of gestation. No adverse effects on reproduction and no teratological changes were noted.

INDICATIONS

Diazepam is indicated for the management of anxiety disorders for the short-term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

NOTE: Because the auto-injector provides a minimum dose of 10 mg diazepam, it should not be used to treat individuals with mild and moderate degrees of anxiety and anxiety related disorders that would ordinarily be managed with intramuscular doses of less than 10 mg.

In acute alcohol withdrawal, diazepam may be useful in the symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis.

As an adjunct prior to endoscopic procedures if apprehension, anxiety or acute stress reactions are present, and to diminish the patient's recall of the procedures (See WARNINGS).

Diazepam is a useful adjunct for the relief of skeletal muscle spasm due to reflex spasm to local pathology (such as inflammation of the muscles or joints, or secondary to trauma), spasticity caused by upper motor neuron disorders (such as cerebral palsy and paraplegia); athetosis; stiff man syndrome; and tetanus.

Diazepam injection is a useful adjunct in status epilepticus and severe recurrent convulsive seizures,

Diazepam is useful pre-medication for relief of anxiety and tension in patients who are to undergo surgical procedures.

CONTRAINDICATIONS

INTRAVENOUS ADMINISTRATION OF DIAZEPAM WITH THE AUTO-INJECTOR IS CONTRAINDICATED.

Diazepam injection is contraindicated in patients with a known hypersensitivity to this drug; acute narrow angle glaucoma; and open angle glaucoma unless patients are receiving appropriate therapy.

WARNINGS

Diazepam Auto-injector is to be administered only by the intramuscular (I.M.) route.

Extreme care must be used in administering injectable diazepam to the elderly, to very ill patients and to those with limited pulmonary reserve because of the possibility that apnea and/or cardiac arrest may occur. Concomitant use of barbiturates, alcohol, or other central nervous system depressants increases depression with increased risk of apnea. Resuscitative equipment including that necessary to support respiration should be readily available.

When diazepam is used with a narcotic analgesic, the dosage of the narcotic should be reduced by at least one-third and administered in small increments. In some cases the use of a narcotic may not be necessary.

Diazepam injection should not be administered to patients in shock, coma, or in acute alcoholic intoxication with depression of vital signs. As is true of most CNS-acting drugs, patients receiving diazepam should be cautioned against engaging in hazardous occupations requiring complete mental alertness, such as operating machinery or driving a motor vehicle.

Tonic status epilepticus has been precipitated in patients treated with I.V. diazepam for petit mal status or petit mal variant status.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of minor tranquilizers (diazepam, meprobamate and chlordiazepoxide) during the first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug.

In humans, measurable amounts of diazepam were found in maternal and cord blood, indicating placental transfer of the drug. Until additional information is available, diazepam injection is not recommended for obstetrical use.

Pediatric Use:

DiaJect delivers a fixed dose of 10 mg diazepam which may be unsuitable for some members of the pediatric population.

Efficacy and safety of parenteral diazepam has not been established in the neonate (30 days or less of age).

Prolonged central nervous system depression has been observed in neonates, apparently due to inability to biotransform diazepam into inactive metabolites.

Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines (see DRUG ABUSE AND DEPENDENCE section).

PRECAUTIONS

Although seizures may be brought under control promptly with a single 10 mg intramuscular dose, a significant proportion of patients may experience a return to seizure activity. Consequently, it may become necessary to re-administer the drug. The cumulative maximum dose of diazepam should not exceed 30 mg; the interval between doses should be no less than 10 minutes. 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 diazepam is to be combined with other psychotropic agents or anticonvulsant drugs, careful consideration should be given to the pharmacology of the agents to be employed - particularly with known compounds which may potentiate the action of diazepam, such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. In highly anxious patients with evidence of accompanying depression, particularly those who may have suicidal tendencies, protective measures may be necessary. 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.

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 countermeasures are recommended.

Until additional information is available, injectable diazepam is not recommended for obstetrical use.

Diazepam injection has produced hypotension or muscular weakness in some patients particularly when used with narcotics, barbiturates or alcohol.

The clearance of diazepam and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

ADVERSE REACTIONS

Side effects most commonly reported were drowsiness, fatigue and ataxia; venous thrombosis and phlebitis at the site of injection. Other adverse reactions less frequently reported include: *CNS*: confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo. *G.I.*: constipation, nausea. *G.U.*: incontinence, changes in libido, urinary retention. *Cardiovascular*: bradycardia, cardiovascular collapse, hypotension. *EENT*: blurred vision, diplopia, nystagmus. *Skin*: 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 diazepam 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.

DRUG ABUSE AND DEPENDENCE

Diazepam injection is classified by the Drug Enforcement Administration as a schedule IV controlled substance.

Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating), have occurred following abrupt discontinuance of diazepam. The more severe withdrawal symptoms have usually been limited to those patients who received excessive doses over an extended period of time.

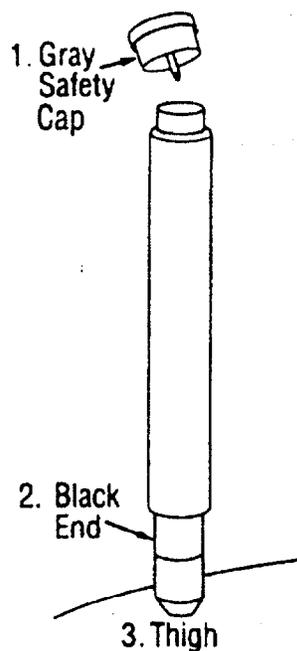
Generally milder withdrawal symptoms (e.g. dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed. 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.

DOSAGE AND ADMINISTRATION (INTRAMUSCULAR ONLY)

DIRECTIONS FOR USE

Detailed instructions for use are available in the Patient Instruction Sheet. General instructions are provided below. When auto-injector use is indicated, proceed as follows:

1. Remove gray safety cap.
2. Place black end on thickest part of thigh (anterior/lateral muscle) and press hard until injector functions.
3. Hold firmly in place for ten seconds, then remove. Massage the area of injection.
4. Bend needle into a hook. Dispose of properly.



Dosage:

Caution: Because the auto-injector automatically delivers a fixed dose of 10 mg of diazepam, it cannot be used in situations requiring lower total doses or those in which small incremental increases of diazepam are required.

The usual recommended dose in older children and adults ranges from 10 mg to 20 mg I.M. depending on the indication and its severity. The cumulative total dose and individual maximum dose for intramuscular administration will vary with the specific indication (See dosage for specific indications).

Intramuscular: When instructions are followed properly the Diazepam Auto-injector injects deeply into the muscle.

Intravenous Use: The Diazepam Autoinjector is not designed or intended for intravenous use.

Severe Anxiety Disorders and Symptoms of anxiety:

- Usual Adult Dosage: 10 mg, I.M. 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.

- Usual Adult Dosage: 10 mg, I.M. initially, then 10 mg in 3 to 4 hours, if necessary.

Endoscopic Procedures: Adjunctively, if apprehension, anxiety or acute stress reactions are present prior to endoscopic procedures. Dosage of narcotics should be reduced by at least a third and in some cases may be omitted. See *Precautions* for peroral procedures.

- Usual Adult Dosage: 10mg I.M., approximately 30 minutes prior to the procedure.

Muscle Spasm: Associated with local pathology, cerebral palsy, athetosis, stiff-man syndrome or tetanus.

- Usual Adult Dosage: 10 mg, I.M., initially, then 10 mg in 3 to 4 hours, if necessary. For tetanus, larger doses may be required.

Status Epilepticus and Severe Recurrent Convulsive Seizures: In the convulsing patient, the I.V. route is preferred. However, if conditions preclude intravenous administration, the I.M. route may be used.

- Usual Adult Dosage: 10 mg, initially. This injection may be repeated if necessary at 10 to 15 minute intervals up to a maximum dose of 30 mg. If necessary, therapy with diazepam may be repeated in 2 to 4 hours; however, residual active metabolites may persist, and re-administration should be made with this consideration.

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

Pre-operative Medication: To relieve anxiety and tension. (if atropine, scopolamine or other premedications are desired, they must be administered in separate syringes).

- Usual Adult Dosage: 10 mg, I.M. (preferred route), before surgery.

General: Once the acute symptomatology has been properly controlled with diazepam injection, the patient may be placed on oral therapy with diazepam if further treatment is required.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever the solution and container permit.

Management 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. General supportive measures should be employed, along with Intravenous fluids, and an adequate airway maintained. Hypotension may be combated by the use of norepinephrine or metaraminol. Dialysis is of limited value.

