**DIAZEPAM TABLETS, USP**

Rx only

**DESCRIPTION**

Diazepam is a benzodiazepine derivative. The chemical name of diazepam is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2,4-benzodiazepin-2-one. It is a colorless, odorless, crystalline compound, insoluble in water. The empirical formula is C<sub>16</sub>H<sub>13</sub>C<sub>IN</sub>2O and the molecular weight is 284.75. The structural formula is as follows:

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Diazepam is available for oral administration as tablets containing 2 mg, 5 mg or 10 mg diazepam. In addition to the active ingredient diazepam, each tablet contains the following inactive ingredients: calcium stearate, colloidal silicon dioxide, lactose monohydrate and microcrystalline cellulose with the following dyes: 5-mg tablets contain D&C Yellow #10 aluminum lake; 10-mg tablets contain FD&C Blue #1 aluminum lake. Diazepam 2-mg tablets contain no dye.
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**PHARMACOLOGY**

**Indications**

Diazepam is a benzodiazepine that exerts anxiolytic, sedative, muscle-relaxant, antidepressant and amnestic effects. Most of these effects are thought to be a result of the facilitation of the action of the neurotransmitter gamma-aminobutyric acid (GABA). The benzodiazepines are used in the following conditions:

1. **Anxiety**
   - Generalized anxiety disorder
   - Social phobia
   - Acute stress reaction
   - Anxiety associated with physical or psychological trauma

2. **Convulsive Disorders**
   - Adjunctive therapy in convulsive disorders, including status epilepticus
   - Treatment for agitation in patients with dementia (e.g., Alzheimer’s disease)

3. **Sleep Disorders**
   - Treatment of insomnia

4. **Anxiolytic Effects**
   - Management of anxiety disorders
   - Management of anxiety associated with physical or psychological trauma

5. **Muscle relaxant**
   - Management of muscle spasticity in patients with cerebral palsy, spinal cord injury, or other neurological disorders

6. **Anticonvulsant**
   - Management of seizures in patients with epilepsy

7. **Antidepressant**
   - Management of minor depressive symptoms

8. **Preoperative Mediation**
   - Reduction of anxiety in patients before major surgical procedures

**Contraindications**

Diazepam is contraindicated in patients with a known hypersensitivity to diazepam or any of its excipients. Diazepam is also contraindicated in patients with myasthenia gravis, severe respiratory insufficiency, severe hepatic insufficiency, and sleep apnea syndrome. It may be used in patients with open-angle glaucoma who are receiving appropriate therapy, but is contraindicated in acute narrow-angle glaucoma.

**Warnings**

Diazepam is not recommended in the treatment of psychotic patients and should not be employed instead of appropriate treatment.

Since diazepam has a central nervous system depressant effect, patients should be advised against the simultaneous ingestion of alcohol and other CNS-depressant drugs during diazepam therapy.

As with other agents that have anticonvulsant activity, when diazepam is used as an adjunct in treating convulsive disorders, the possibility of an increase in the frequency and/or severity of grand mal seizures may require an increase in the dosage of standard anticonvulsant medication. Abrupt withdrawal of diazepam in such cases may also be associated with a temporary increase in the frequency and/or severity of seizures.

**Pregnancy**

An increased risk of congenital malformations and other developmental abnormalities associated with the use of benzodiazepines during pregnancy has been suggested. There have been reports of neonatal flaccidity, respiratory and feeding difficulties, and hypothermia in children born to mothers who have been receiving benzodiazepines late in pregnancy. In addition, children born to mothers receiving benzodiazepines on a regular basis late in pregnancy may be at some risk of experiencing withdrawal symptoms during the postnatal period.

Diazepam has been shown to be teratogenic in mice and hamsters when given orally at daily doses of 100 mg/kg or greater (approximately eight times the maximum recommended human dose [MRHD=1 mg/kg/day] or greater on a mg/m² basis). Cleft palate and encephalopathy are the most common and consistently reported malformations produced in these species by administration of benzodiazepines at maternally toxic doses of diazepam during organogenesis. Rodent studies have indicated that prenatal exposure to diazepam does not appear to cause any abnormalities that can produce long-term changes in cellular immune responses, brain neurochemistry, and behavior.

In general, the use of diazepam in women of childbearing potential, and more specifically during pregnancy, should be considered only when the clinical situation warrants the risk to the fetus. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered.

**Drug Interactions**

Conflicting information has been published on changes of plasma protein binding in patients taking diazepam. It is recommended that patients be discontinued. These reactions are more likely to occur in children and the elderly.

A lower dose is recommended for patients with chronic respiratory insufficiency, due to the risk of respiratory depression.

Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse (see Drug Interactions).

In debilitated patients, it is recommended that the dosage be limited to the smallest effective amount to prevent the development of tolerance or dependence.

Some loss of response to the effects of benzodiazepines may develop after repeated use of diazepam for a prolonged time.

**Information for Patients**

To assure the safe and effective use of diazepam, patients should be informed that, since benzodiazepines may produce psychological and physical dependence, it is advisable that they consult with their physician before either increasing the dose or abruptly discontinuing this drug. The risk of dependence increases with duration of treatment; it is also greater in patients with a history of alcohol or drug abuse.

Patients should be advised against the simultaneous ingestion of alcohol and other CNS-depressant drugs during diazepam therapy. It is advisible that they consult with their physician before either increasing the dose or abruptly discontinuing this drug.

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**Drug Interactions**

Central Nervous System (CNS) Depressants

Patients receiving diazepam should be advised against driving hazardous occupations requiring complete mental alertness, such as operating machinery or driving a motor vehicle.

**Nursing Mothers**

Diazepam passes into breast milk. Breastfeeding is therefore not recommended in patients receiving diazepam.

**Avoidance of Reactions**

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Patients should also be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physician about the desirability of discontinuing the drug.

**Labor and Delivery**

Special care must be taken when diazepam is used during labor and delivery, as high single doses may produce irregularities in the fetal heart rate in the fetus of a diabetic or a polyhydramnios mother. Diazepam is not recommended in the treatment of psychotic patients and should not be employed instead of appropriate treatment.

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Alcohol

Concurrent use with alcohol is not recommended due to enhancement of the sedative effect.

Antacids

Diazepam peak concentrations are 30% lower when antacids are administered concurrently. However, there is no effect on the extent of absorption. The lower peak concentrations appear due to a slower rate of absorption, with the time required to achieve peak concentrations on average 20 to 25 minutes greater in the presence of antacids. However, this difference was not statistically significant.

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 concomitant administration of the pharmacokinetics of diazepam may lead to increased and prolonged sedation. At present, this reaction is known to occur with cimetidine, ketocazole, fluvoxamine, fluoxetine, and omeprazole.

Phenytion

There have also been reports that the metabolic elimination of phenytoin is decreased by diazepam.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In studies in which mice and rats were administered diazepam in the diet at a dose of 75 mg/kg/day (approximately 6 and 12 times, respectively, the maximum recommended human dose [MRHD=1 mg/kg/day] on a mg/m² basis) for 80 and 104 weeks, respectively, an increased incidence of liver tumors was observed in male and female rats. The data currently available are inadequate to determine the mutagenic potential of diazepam. Reproduction studies in rats showed decreases in the number of pregnancies and in the number of surviving offspring following administration of an oral dose of 100 mg/kg/day (approximately 16 times the MRHD on a mg/m² basis) prior to and during mating and throughout gestation and lactation. No adverse effects on fertility or offspring viability were noted at a dose of 80 mg/kg/day (approximately 13 times the MRHD on a mg/m² basis).

Pregnancy

Category D (see WARNINGS: Pregnancy).

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 6 months have not been established.

Geriatric Use

In elderly patients, it is recommended that the dosage be limited to the smallest effective amount to preclude the development of ataxia or overestimation (2 mg 2.5 mg once or twice daily, initially to be increased gradually as needed and tolerated).

Extended accumulation of diazepam and its major metabolite, desmethyldiazepam, has been noted following chronic administration of diazepam in healthy elderly male subjects. Metabolites of this drug are known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Hepatic Insufficiency

Decreases in clearance and protein binding, and increases in volume of distribution and half-life have 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 this active metabolite of the diazepam. Benzodiazepines are commonly implicated in hepatic encephalopathy. Increases in half-life have also been noted in geriatric patients and in both acute and chronic hepatitis (see CLINICAL PHARMACOLOGY: Pharmacokinetics in Special Populations: Hepatic Insufficiency).

ADVERSE REACTIONS

Side effects most commonly reported were drowsiness, fatigue, muscle weakness, and ataxia. The following have also been reported:

Central Nervous System:

confusion, depression, dysyria, headache, slurred speech, tremor, vertigo

Gastrointestinal System:

constipation, nausea, gastrointestinal disturbances

Special Senses:

blurred vision, diplopia, dizziness

Cardiovascular System:

hypotension

Psychiatric and Paradoxical Reactions:

stimulation, restlessness, acute hyperexcitability, states, anxiety, agitation, aggressiveness, irritability, rage, hallucinations, psychoses, delusions, increased muscle spasticity, insomnia, sleep disturbances, and nightmares. Inappropriate behavior and other adverse behavioral effects may be reported when used with benzodiazepines. Should these occur, use of the drug should be discontinued. They are more likely to occur in children and in the elderly.

Urgent System:

incontinence, changes in libido, urinary retention

Skin and Appendages:

skin rashes

Laboratories:

elevated transaminases and alkaline phosphatase

Other:

changes in salivation, including dry mouth, hypersalivation

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

Postmarketing Experience:

Injury, Poisoning and Procedural Complications:

There have been reports of falls and fractures in benzodiazepine users. The risk is increased in those taking concomitant sedatives (including alcohol), and in the elderly.

DRUG ABUSE AND DEPENDENCE

Diazepam is subject to Schedule IV control under the Controlled Substances Act of 1970. Abuse and dependence of benzodiazepines have been reported. Addiction potential occurs (such as drug addiction or alcoholism) should be under careful surveillance when receiving diazepam or other psychotropic agents because of the predisposition of such patients to habituation and dependence. Once physical dependence to benzodiazepines has developed, termination of treatment will be accompanied by withdrawal symptoms. The risk is more pronounced in patients on long-term therapy.

Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of diazepam. These withdrawal symptoms include ataxia, tremor, abdominal and muscle tremors, vomiting, sweating, headache, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases, the following symptoms may occur: depression, derealization, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or illusions. The more severe withdrawal symptoms have usually been limited to those patients who had 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 termination of therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed.

Chronic use (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena.

Rebound Anxiety: A transient syndrome whereby the symptoms that led to treatment with diazepam recur in an enhanced form. This may occur upon discontinuation of treatment. It may be accompanied by other reactions including mood change, anxiety, and irritability.

Since the risk of withdrawal phenomena and rebound phenomena is greater after abrupt discontinuance of treatment, it is recommended that the dosage be decreased gradually.

OVERDOSAGE

Overdose of benzodiazepines is usually manifested by central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, confusion, and lethargy. In more serious cases, symptoms may include ataxia, disorientation, hypotension, respiratory depression, coma (rarely), and death (very rarely). Overdose of benzodiazepines in combination with other CNS depressants (including alcohol) may be fatal and should be closely monitored.

Management of Overdose

Following overdose with oral benzodiazepines, general supportive measures should be employed including the monitoring of respiration, pulse, and blood pressure. Vomiting should be induced (within 1 hour) if the patient is conscious. Gastric lavage should be undertaken with the airway protected if the patient is unconscious. Intravenous fluids should be administered. If there is no advantage in emptied the stomach, activated charcoal should be given to reduce absorption.

Special attention should be paid to respiratory and cardiac function in intensive care. General supportive measures should be employed, along with intravenous fluids, and an adequate airway maintained. Should hypotension develop, treatment may include intravenous fluid therapy, repositioning, judicious use of vasopressors appropriate to the clinical situation, if indicated, and other appropriate countermeasures. Dialysis is of limited value.

As with the management of intentional overdosage with any drug, it should be considered that multiple agents may have been ingested.

Flumazenil, because it is a selective 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, necessary measures should be instituted to secure airway, ventilation and intravenous access. Flumazenil is intended as an adjunct to, not as 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.

The prescriber should be aware of the risk of seizures in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose. Caution should be observed in the use of flumazenil in epileptic patients treated with benzodiazepines. The complete flumazenil package insert, including CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS, should be consulted prior to use.

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

DOSE AND ADMINISTRATION

DOSAGE should be individualized to the maximum beneficial effect. While the usual daily dosage below will meet the needs of most patients, there will be some who may require higher doses. In such cases, dosage should be increased cautiously to avoid adverse effects.

ADULTS:

Management of Anxiety Disorders and Relief of Symptoms of Anxiety:

SYMPOMATIC RELIEF

10 mg, 3 or 4 times during the first 24 hours, reducing to 5 mg, 3 or 4 times daily as needed

Adjunctively for Relief of Skeletal Muscle Spasm

2 mg to 10 mg, 3 or 4 times daily

Adjunctively in Convulsive Disorders

2 mg to 10 mg, 2 to 4 times daily

GERIATRIC PATIENTS, or in the presence of debilitating disease.

PEDiATRIC PATIENTS:

Because of varied responses to CNS-acting drugs, initiation therapy with lowest dose and increase as required. Not for use in pediatric patients under 6 months.

HOW SUPPLIED

For oral administration, Diazepam Tablets, USP are supplied as:

2 mg: white, flat-faced beveled edge scored tablets, debossed “2682” on one side and “V” on the reverse side, supplied in bottles of 10, 30, 60, 100, 500 and 1000

5 mg: yellow, flat-faced beveled edge scored tablets, debossed “2682” on one side and “V” on the reverse side, supplied in bottles of 10, 30, 60, 90, 100, 120, 500, 1000 and 5000

10 mg: blue, flat-faced beveled edge scored tablets, debossed “2684” on one side and “V” on the reverse side, supplied in bottles of 10, 30, 60, 90, 100, 120, 500, 1000 and 5000

STORAGE

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. Dispense in tight, light-resistant containers as defined in USP/NF.

Manufactured for:

QUALITEST PHARMACEUTICALS

Huntsville, AL 35811

8181922 R4 Diaz_Flat size: 7.75 x 11 Fold to: 1.125 x 1.125 1/31/14 4:07 AM Page 2