

PRODUCT MONOGRAPH

^{Pr}pms-DIAZEPAM

Diazepam Tablets, USP
2 mg, 5 mg and 10 mg

Anxiolytic-Relaxant

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THERAPEUTIC CLASSIFICATION

Anxiolytic-Relaxant

ACTION

Diazepam possesses anxiolytic and sedative properties useful in the symptomatic relief of manifest anxiety and tension states. It has also an adjunctive value in the relief of certain neurospastic conditions. Peak Diazepam blood levels after oral administration of Diazepam tablets are reached within one to two hours after single oral dosing. The half-life is six to eight hours with a slower decline thereafter, possibly due to tissue storage. However, after repeated doses, blood levels increase significantly over a period of 24-48 hours. In humans, comparable blood levels of Diazepam were obtained in maternal and cord blood indicating placental transfer of the drug.

INDICATIONS AND CLINICAL USE

pms-Diazepam (Diazepam) is useful in the symptomatic relief of excessive anxiety and tension resulting from stressful circumstances including those anxiety states associated with somatic

manifestations.

It is useful in the symptomatic management of mild to moderate psychoneurotic states manifested by tension, anxiety, excitation, apprehension, agitation and phobia.

In acute alcoholic, withdrawal, pms-Diazepam (Diazepam) may be useful in the symptomatic relief of acute agitation tremor and impending acute delirium tremors.

It is a useful adjunct to the relief of spasticity in neuromuscular disorders, such as cerebral palsy, athetosis and for the relief of skeletal muscle spasm due to local pathology such as inflammation of the muscles or joints or secondary to trauma.

It may be used adjunctively in convulsive disorders, although it is not effective as a sole therapy.

WARNINGS

Diazepam is not of value in the treatment of psychotic patients and should not be administered in lieu of the required treatment.

Patients should be cautioned against participation in hazardous occupations or those requiring mental alertness such as operating machinery or driving a motor vehicle.

Patients should be advised against the simultaneous ingestion of alcohol and other CNS depressant drugs during Diazepam therapy, since it is a CNS depressant.

Abrupt withdrawal of Diazepam when used as an adjunct in treating convulsive disorders may be associated with a temporary increase in the frequency and /or severity of seizures

DRUG DEPENDENCE

Abrupt cessation of large doses of Diazepam after prolonged periods may precipitate acute withdrawal symptoms (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating) in these cases, the drug should be discontinued gradually. These withdrawal symptoms are usually limited to patients who had received excessive doses over an extended length of time. Caution should be exercised when it is considered necessary to administer Diazepam to addiction prone individuals because of the predisposition of such patients to habituation and dependency.

USE IN PREGNANCY

Diazepam should not be used during the first trimester of pregnancy except if absolutely necessary.

PRECAUTIONS

POTENTIATION OF DRUG EFFECTS

Careful consideration should be given if Diazepam 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. Since Diazepam has a central nervous system depressant effect, patients should be advised against the simultaneous ingestion of alcohol and other central nervous system depressant drugs during Diazepam therapy.

USE IN ELDERLY

Elderly and debilitated patients or those with organic brain disorders have been found to be prone to central nervous system depression following even low doses of Diazepam. For these patients it is recommended that the dosage be limited to the smallest effective amount to

preclude development of ataxia, oversedation or other possible adverse effects.

USE IN EMOTIONAL DISORDERS

Diazepam 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, associated with suicidal tendencies.

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

USE IN EPILEPTIC PATIENTS

Diazepam may exacerbate grand mal seizures in some patients, caution is required when it is used in epileptic patients. An adjustment may be necessary in their anti-convulsive medication. Abrupt withdrawal of diazepam in these patients should also be avoided.

The usual precautions in treatment of patients with impaired renal and hepatic functions should be observed. If Diazepam is administered for protracted periods, periodic blood counts and liver function tests would be highly advisable.

ADVERSE REACTIONS

The most common adverse reactions reported for Diazepam 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 and changes in libido.

The most serious adverse reactions occasionally reported are leucopenia, jaundice, hypersensitivity and paradoxical reactions (such as hyperexcited states, anxiety, excitement, hallucinations, increased muscle spasticity, insomnia, rage, as well as sleep disturbances and stimulation), should these occur, the drug should be discontinued. Minor changes in EEC patterns have been observed in patients on Diazepam therapy.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The main symptoms of overdosage include: drowsiness, ataxia, confusion, somnolence, diminished reflexes and coma. There are minimum effects on respiration, pulse and blood pressure unless the overdosage is extreme.

There is no specific antidote known. Gastric lavage may be beneficial if performed soon after oral ingestion of Diazepam. 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 or metaraminol bitartrate for hypotension. Dialysis appears to be of little value.

DOSAGE & ADMINISTRATION

Dosage schedule should be flexible to accommodate individual requirements on the basis of individual diagnosis, severity of symptoms and degree of response. While the usual daily dosages given below will meet the needs of most patients, there will be some who may require higher dosage. In such cases, dosage should be increased with caution to avoid the occurrence of adverse effects due to a cumulative effect of the drug which may occur in the first few days of administration. Therefore, the dosage should be increased only after the stabilization is evident.

ADULTS

Usual daily dosage.

SYMPTOMATIC RELIEF OF ANXIETY AND TENSION IN PSYCHNEUROSIS-ANXIETY REACTIONS

2 to 10 mg, 2 to 4 times daily depending upon severity of symptoms.

SYMPTOMATIC RELIEF IN ACUTE ALCOHOLIC WITHDRAWAL

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 to 10 mg, 3 to 4 times daily.

ELDERLY AND DEBILITATED PATIENTS, OR IN THE PRESENCE OF DEBILITATING DISEASE

2 mg to 2.5 mg, 1 to 2 times daily initially; increase gradually as needed and tolerated.

CHILDREN

Because of varied responses to CNS depressing drugs, initiate therapy with lowest dose and increase as required. Not for use in children under 6 months:

1 to 2.5 mg, 3 or 4 times daily initially; increase gradually as needed or tolerated.

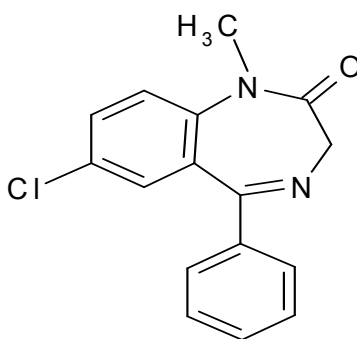
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Common Name: Diazepam

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

Structural Formula:



Molecular Formula: $C_{16}H_{13}ClN_2O$

Molecular Weight: 284.74 g/mol

Description: Colourless, crystalline compound

Solubility: Insoluble in water

Composition: pms-DIAZEPAM tablets contain diazepam and the following non-medicinal ingredients: Starch 1500, Magnesium Stearate, Colloidal Silicon Dioxide, Microcrystalline Cellulose and Lactose (spray dried). The 5 mg tablets contain FD & C Yellow #6 Alum. Lake (15%), and D & C Yellow

#10 Alum. Lake (17%). The 10 mg tablets contain FD & C Blue #1 Alum. Lake (10%).

Stability and Storage: pms-DIAZEPAM tablets should be stored below 40°C, preferably between 15-30°C, in a tight, light-resistant container.

AVAILABILITY OF DOSAGE FORMS

2 mg Tablets: Each white scored tablet, identified p/2, contains 2 mg Diazepam USP.

5 mg Tablets: Each yellow scored tablet, identified p/5, contains 5 mg Diazepam USP.

10 mg Tablets: Each blue scored tablet, identified p/10, contains 10 mg Diazepam USP.

All strengths are available in bottles of 50, 100, 500 and 1000 tablets

PHARMACOLOGY

Diazepam is a benzodiazepine with CNS depressant properties.

In laboratory animal studies diazepam at low doses (0.5mg/kg i.p) appears to depress the electrical activity of the brain, especially the hippocampus, without depressing the cortex. The animal therefore remains alert. Only at higher doses (5.0 mg/kg) there was a depression of the electrical discharge from the cortex, hippocampus amygdala and septum, resulting in ataxia and sleep. Diazepam did not demonstrate the autonomic blocking action or extrapyramidal effects characteristic of barbiturates, chlorpromazine and reserpine. In the dog, diazepam was found to exhibit only a slight, transient cardio-vascular depressor effects.

In laboratory animals it produces, in varying doses, taming, desinhibitory, sedative,

anticonvulsant, muscle relaxant, ataxia and hypnotic 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 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 behavioral 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 electro shock convulsions and relatively ineffective against minimal electro shock convulsions.

It reduces body tone in the cat 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 hippocampus in the cat and monkey. It also depresses the cardio-vascular 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 1-2 hours after administration. The half-life is 6-8 hours with a slower decline thereafter, possibly due to tissue

storage. In man, oral administration of radio labelled Diazepam H³ at a dose of 10 mg, 70% was excreted in urine (excretion rate half-life was 3 days) and only 10% was excreted in the feces. The peak levels of blood H³ occurred in 2-4 hours.

TOXICOLOGY

ACUTE TOXICOLOGY

Acute Toxicity studies in laboratory animals are reported as follows:

| Species | Route | LD₅₀ Dose (mg/kg) |
|----------------|--------------|-------------------------------------|
| Mice | p.o. | 720 |
| | i.p. | 220 |
| | s.c. | > 800 |
| | i.v. | > 100 |
| Rat | p.o. | 1800 |
| | i.v. | 32 |
| Rabbit | p.o. | 328 |

SUB-ACUTE TOXICITY

Diazepam at a dose of 1000 mg/kg administered to rats as a dietary admixture for the period of 6 weeks, showed a decrease in growth and appetite but no significant effect on blood dyscrasias or tissue changes.

CHRONIC TOXICOLOGY

In a forty-two week chronic toxicity study in rats diazepam was administered in dose ranges of up to 240 mg/kg. There were no abnormalities observed in respect to the rats normal growth, food consumption, blood counts and gross microscopic findings.

A series of chronic toxicity studies were conducted in a number of species including rats, dogs and marmosets. In the rat experiments, diazepam doses of up to 320 mg/kg were used for one year. In the dog and the marmoset doses of up to 40 mg/kg were utilized for six and three months respectively.

In the rat growth was regular and untowards effects of sedation and ataxia did not occur in these animals. Blood counts including the determinations of the hematocrit, hemoglobin, total and differential leukocytes did not reveal abnormalities caused by prolonged treatment. Gross and microscopic tissue changes related to treatment with diazepam were not observed following sacrifice.

Dogs receiving diazepam showed moderate sedation with the highest dose and one animal expired after 22 Weeks of treatment following an episode of maximal convulsive seizures. Clinical laboratory findings were essentially normal in all groups. Similar to the dog, in the marmoset a marked sedation was also observed in this species characterized by pronounced taming activity. However, untowards reactions did not occur in these animals.

TERATOLOGY

Reproductive studies have been performed on rats with diazepam in oral doses of 1, 10, 80 & 100 mg/kg. Following were the results obtained:

Diazepam at the lower dose levels had no effect on the mortality rate and survival of offsprings.

Diazepam at the dose level of up to and including 80 mg/kg had no significant teratological effect on the offsprings.

Diazepam at the dose level of 100 mg/kg showed a decrease in the number of pregnancies and a reduction of surviving offsprings. Skeletal and other deformities were observed in several neonates.