

Diazepam

Introduction: Diazepam is a benzodiazepine derivative.

Mechanism of action: Diazepam is a benzodiazepine that binds to a specific subunit on the GABA receptor at a site that is distinct from the binding site of the endogenous GABA molecule. The GABA receptor is an inhibitory channel which, when activated, decreases neuronal activity. Because of the role of diazepam as a positive allosteric modulator of GABA, when it binds to benzodiazepine receptors it causes inhibitory effects. This arises from the hyperpolarization of the post-synaptic membrane owing to the control exerted over negative chloride ions by GABA_A receptors. Benzodiazepines including diazepam however, do not have any effect on the levels of GABA in the brain. Diazepam appears to act on areas of the limbic system, thalamus and hypothalamus, inducing anxiolytic effects. Its actions are due to the enhancement of GABA activity. Benzodiazepine drugs including diazepam increase the inhibitory processes in the cerebral cortex.

Pharmacology:

Absorption: After oral administration > 90% of diazepam is absorbed and the average time to achieve peak plasma concentrations is 1 - 1.5 hours with a range of 0.25 to 2.5 hours

Distribution: Diazepam and its metabolites are highly bound to plasma proteins (diazepam 98%). Diazepam and its metabolites cross the blood-brain and placental barriers and are also found in breast milk in concentrations approximately one tenth of those in maternal plasma (days 3 to 9 post-partum). In young healthy males, the volume of distribution at steady-state is 0.8 to 1.0 L/kg.

Metabolism: Diazepam is N-demethylated by CYP3A4 and 2C19 to the active metabolite N-desmethyldiazepam, and is hydroxylated by CYP3A4 to the active metabolite temazepam. N-desmethyldiazepam and temazepam are both further metabolized to oxazepam. Temazepam and oxazepam are largely eliminated by glucuronidation.

Elimination: The initial distribution phase is followed by a prolonged terminal elimination phase (half-life up to 48 hours). The terminal elimination half-life of the active metabolite N-desmethyldiazepam is up to 100 hours. Diazepam and its metabolites are excreted mainly in the urine, predominantly as their glucuronide conjugates. The clearance of diazepam is 20 to 30 mL/min in young adults.

Indications: Diazepam Tablets are indicated for the management of anxiety disorders or 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. In acute alcohol withdrawal, diazepam may be useful in the symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis. 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; and stiff-man syndrome.

Dosage: Dosage should be individualized for maximum beneficial effect. While the usual daily dosages given 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:	Usual Daily Dose
<i>Management of Anxiety Disorders and relief of Symptoms of Anxiety.</i>	Depending on severity of symptoms — 2 mg to 10 mg, 2 to 4 times daily
<i>Symptomatic Relief in Acute Alcohol Withdrawal.</i>	10 mg, 3 or 4 times during the first 24 hours, reducing to 5 mg, 3 or 4 times daily as needed
<i>Adjunctively for Relief of Skeletal Muscle Spasm.</i>	2 mg to 10 mg, 3 or 4 times daily
<i>Adjunctively in Convulsive Disorders</i>	2 mg to 10 mg, 2 to 4 times daily
<i>Geriatric Patients, or in the presence of debilitating disease.</i>	2 mg to 2 ½ mg, 1 or 2 times daily initially; increase gradually as needed and tolerated
Children:	
Because of varied responses to CNS-acting drugs, initiate therapy with lowest dose and increase as required. Not for use in children under 6 months.	1 mg to 2 ½ mg, 3 or 4 times daily initially; increase gradually as needed and tolerated

Side effects: Side effects most commonly reported were drowsiness, fatigue and ataxia. Infrequently encountered were confusion, constipation, depression, diplopia, dysarthria, headache, hypotension, incontinence, jaundice, changes in libido, nausea, changes in salivation, skin rash, slurred speech, tremor, urinary retention, vertigo and blurred vision. 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.

Precautions:

General: 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 that may potentiate the action of diazepam, such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. The usual precautions are indicated for severely depressed patients or those in whom there is any evidence of latent depression or anxiety associated with depression, particularly the recognition that suicidal tendencies may be present and protective measures may be necessary. Psychiatric and paradoxical reactions are known to occur when using benzodiazepines. 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.

Pregnancy: An increased risk of congenital malformations and other developmental abnormalities associated with the use of benzodiazepine drugs during pregnancy has been suggested

Nursing Mothers: Diazepam passes into breast milk. Breastfeeding is therefore not recommended in patients receiving Diazepam.

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 over sedation (2 mg to 2.5 mg once or twice daily, initially to be increased gradually as needed and tolerated).

Extensive accumulation of diazepam and its major metabolite, desmethyldiazepam, has been noted following chronic administration of diazepam in healthy elderly male subjects.

Hepatic Insufficiency: Decreases in clearance and protein binding, and increases in volume of distribution and half-life has 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 the active metabolite desmethyldiazepam. Benzodiazepines are commonly implicated in hepatic encephalopathy. Increases in half-life have also been reported in hepatic fibrosis and in both acute and chronic hepatitis

Contraindications: Diazepam is contraindicated in patients with a known hypersensitivity to diazepam and, because of lack of sufficient clinical experience, in pediatric patients under 6 months of age. 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.

How supplied: Customized as per request.