

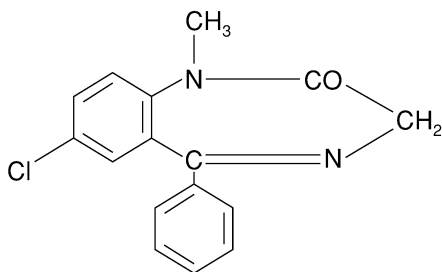


VALIUM
brand of
diazepam
TABLETS

R_x Only

DESCRIPTION

Valium (diazepam) is a benzodiazepine derivative. The chemical name of diazepam is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. It is a colorless to light yellow crystalline compound, insoluble in water. The empirical formula is C₁₆H₁₃ClN₂O and the molecular weight is 284.75. The structural formula is as follows:



Valium 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: anhydrous lactose, corn starch, pregelatinized starch and calcium stearate with the following dyes: 5-mg tablets contain FD&C Yellow No. 6 and D&C Yellow No. 10; 10-mg tablets contain FD&C Blue No. 1. Valium 2-mg tablets contain no dye.

CLINICAL PHARMACOLOGY

Diazepam is a benzodiazepine that exerts anxiolytic, sedative, muscle-relaxant, anticonvulsant and amnesic effects. Most of these effects are thought to result from a facilitation of the action of gamma aminobutyric acid (GABA), an inhibitory neurotransmitter in the central nervous system.

Pharmacokinetics

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. Absorption is delayed and decreased when administered with a moderate fat meal. In the presence of food mean lag times are approximately

32 45 minutes as compared with 15 minutes when fasting. There is also an
33 increase in the average time to achieve peak concentrations to about 2.5 hours
34 in the presence of food as compared with 1.25 hours when fasting. This results
35 in an average decrease in C_{max} of 20% in addition to a 27% decrease in AUC
36 (range 15% to 50%) when administered with food.

37 **Distribution**

38 Diazepam and its metabolites are highly bound to plasma proteins (diazepam
39 98%). Diazepam and its metabolites cross the blood-brain and placental
40 barriers and are also found in breast milk in concentrations approximately one
41 tenth of those in maternal plasma (days 3 to 9 post-partum). In young healthy
42 males, the volume of distribution at steady-state is 0.8 to 1.0 L/kg. The decline
43 in the plasma concentration-time profile after oral administration is biphasic.
44 The initial distribution phase has a half-life of approximately 1 hour, although
45 it may range up to >3 hours.

46 **Metabolism**

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

52 **Elimination**

53 The initial distribution phase is followed by a prolonged terminal elimination
54 phase (half-life up to 48 hours). The terminal elimination half-life of the
55 active metabolite N-desmethyldiazepam is up to 100 hours. Diazepam and its
56 metabolites are excreted mainly in the urine, predominantly as their
57 glucuronide conjugates. The clearance of diazepam is 20 to 30 mL/min in
58 young adults. Diazepam accumulates upon multiple dosing and there is some
59 evidence that the terminal elimination half-life is slightly prolonged.

60 **Pharmacokinetics in Special Populations**

61 *Children*

62 In children 3 - 8 years old the mean half-life of diazepam has been reported to
63 be 18 hours.

64 *Newborns*

65 In full term infants, elimination half-lives around 30 hours have been reported,
66 with a longer average half-life of 54 hours reported in premature infants of 28
67 - 34 weeks gestational age and 8 - 81 days post-partum. In both premature and
68 full term infants the active metabolite desmethyldiazepam shows evidence of
69 continued accumulation compared to children. Longer half-lives in infants
70 may be due to incomplete maturation of metabolic pathways.

71 *Geriatric*

72 Elimination half-life increases by approximately 1 hour for each year of age
73 beginning with a half-life of 20 hours at 20 years of age. This appears to be
74 due to an increase in volume of distribution with age and a decrease in
75 clearance. Consequently, the elderly may have lower peak concentrations, and
76 on multiple dosing higher trough concentrations. It will also take longer to
77 reach steady-state. Conflicting information has been published on changes of
78 plasma protein binding in the elderly. Reported changes in free drug may be
79 due to significant decreases in plasma proteins due to causes other than simply
80 aging.

81 *Hepatic Insufficiency*

82 In mild and moderate cirrhosis, average half-life is increased. The average
83 increase has been variously reported from 2-fold to 5-fold, with individual
84 half-lives over 500 hours reported. There is also an increase in volume of
85 distribution, and average clearance decreases by almost half. Mean half-life is
86 also prolonged with hepatic fibrosis to 90 hours (range 66 - 104 hours), with
87 chronic active hepatitis to 60 hours (range 26 - 76 hours), and with acute viral
88 hepatitis to 74 hours (range 49 - 129). In chronic active hepatitis, clearance is
89 decreased by almost half.

90 **INDICATIONS**

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

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

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

101 Oral Valium may be used adjunctively in convulsive disorders, although it has
102 not proved useful as the sole therapy.

103 The effectiveness of Valium in long-term use, that is, more than 4 months, has
104 not been assessed by systematic clinical studies. The physician should
105 periodically reassess the usefulness of the drug for the individual patient.

106 **CONTRAINDICATIONS**

107 Valium is contraindicated in patients with a known hypersensitivity to
108 diazepam and, because of lack of sufficient clinical experience, in pediatric
109 patients under 6 months of age. Valium is also contraindicated in patients with
110 myasthenia gravis, severe respiratory insufficiency, severe hepatic

111 insufficiency, and sleep apnea syndrome. It may be used in patients with
112 open-angle glaucoma who are receiving appropriate therapy, but is
113 contraindicated in acute narrow-angle glaucoma.

114 **WARNINGS**

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

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

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

126 **Pregnancy**

127 An increased risk of congenital malformations and other developmental
128 abnormalities associated with the use of benzodiazepine drugs during
129 pregnancy has been suggested. There may also be non-teratogenic risks
130 associated with the use of benzodiazepines during pregnancy. There have
131 been reports of neonatal flaccidity, respiratory and feeding difficulties, and
132 hypothermia in children born to mothers who have been receiving
133 benzodiazepines late in pregnancy. In addition, children born to mothers
134 receiving benzodiazepines on a regular basis late in pregnancy may be at some
135 risk of experiencing withdrawal symptoms during the postnatal period.

136 Diazepam has been shown to be teratogenic in mice and hamsters when given
137 orally at daily doses of 100 mg/kg or greater (approximately eight times the
138 maximum recommended human dose [MRHD=1 mg/kg/day] or greater on a
139 mg/m² basis). Cleft palate and encephalopathy are the most common and
140 consistently reported malformations produced in these species by
141 administration of high, maternally toxic doses of diazepam during
142 organogenesis. Rodent studies have indicated that prenatal exposure to
143 diazepam doses similar to those used clinically can produce long-term
144 changes in cellular immune responses, brain neurochemistry, and behavior.

145 In general, the use of diazepam in women of childbearing potential, and more
146 specifically during known pregnancy, should be considered only when the
147 clinical situation warrants the risk to the fetus. The possibility that a woman of
148 childbearing potential may be pregnant at the time of institution of therapy
149 should be considered. If this drug is used during pregnancy, or if the patient
150 becomes pregnant while taking this drug, the patient should be apprised of the
151 potential hazard to the fetus. Patients should also be advised that if they

152 become pregnant during therapy or intend to become pregnant they should
153 communicate with their physician about the desirability of discontinuing the
154 drug.

155 **Labor and Delivery**

156 Special care must be taken when Valium is used during labor and delivery, as
157 high single doses may produce irregularities in the fetal heart rate and
158 hypotonia, poor sucking, hypothermia, and moderate respiratory depression in
159 the neonates. With newborn infants it must be remembered that the enzyme
160 system involved in the breakdown of the drug is not yet fully developed
161 (especially in premature infants).

162 **Nursing Mothers**

163 Diazepam passes into breast milk. Breastfeeding is therefore not
164 recommended in patients receiving Valium.

165 **PRECAUTIONS**

166 **General**

167 If Valium is to be combined with other psychotropic agents or anticonvulsant
168 drugs, careful consideration should be given to the pharmacology of the
169 agents to be employed - particularly with known compounds that may
170 potentiate the action of diazepam, such as phenothiazines, narcotics,
171 barbiturates, MAO inhibitors and other antidepressants (see **Drug**
172 **Interactions**).

173 The usual precautions are indicated for severely depressed patients or those in
174 whom there is any evidence of latent depression or anxiety associated with
175 depression, particularly the recognition that suicidal tendencies may be
176 present and protective measures may be necessary.

177 Psychiatric and paradoxical reactions are known to occur when using
178 benzodiazepines (see **ADVERSE REACTIONS**). Should this occur, use of
179 the drug should be discontinued. These reactions are more likely to occur in
180 children and the elderly.

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

183 Benzodiazepines should be used with extreme caution in patients with a
184 history of alcohol or drug abuse (see **DRUG ABUSE AND**
185 **DEPENDENCE**).

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

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

192 **Information for Patients**

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

199 Patients should be advised against the simultaneous ingestion of alcohol and
200 other CNS-depressant drugs during Valium therapy. As is true of most CNS-
201 acting drugs, patients receiving Valium should be cautioned against engaging
202 in hazardous occupations requiring complete mental alertness, such as
203 operating machinery or driving a motor vehicle.

204 **Drug Interactions**

205 **Centrally Acting Agents**

206 If Valium is to be combined with other centrally acting agents, careful
207 consideration should be given to the pharmacology of the agents employed
208 particularly with compounds that may potentiate or be potentiated by the
209 action of Valium, such as phenothiazines, antipsychotics,
210 anxiolytics/sedatives, hypnotics, anticonvulsants, narcotic analgesics,
211 anesthetics, sedative antihistamines, narcotics, barbiturates, MAO inhibitors
212 and other antidepressants.

213 **Alcohol**

214 Concomitant use with alcohol is not recommended due to enhancement of the
215 sedative effect.

216 **Antacids**

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

223 **Compounds Which Inhibit Certain Hepatic Enzymes**

224 There is a potentially relevant interaction between diazepam and compounds
225 which inhibit certain hepatic enzymes (particularly cytochrome P450 3A and
226 2C19). Data indicate that these compounds influence the pharmacokinetics of
227 diazepam and may lead to increased and prolonged sedation. At present, this

228 reaction is known to occur with cimetidine, ketoconazole, fluvoxamine,
229 fluoxetine, and omeprazole.

230 Phenytoin

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

233 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

246 **Pregnancy**

247 **Category D** (see **WARNINGS: Pregnancy**).

248 **Pediatric Use**

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

251 **Geriatric Use**

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

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

263 **Hepatic Insufficiency**

264 Decreases in clearance and protein binding, and increases in volume of
265 distribution and half-life has been reported in patients with cirrhosis. In such

266 patients, a 2- to 5- fold increase in mean half-life has been reported. Delayed
267 elimination has also been reported for the active metabolite
268 desmethyldiazepam. Benzodiazepines are commonly implicated in hepatic
269 encephalopathy. Increases in half-life have also been reported in hepatic
270 fibrosis and in both acute and chronic hepatitis (see **CLINICAL**
271 **PHARMACOLOGY: Pharmacokinetics in Special Populations: Hepatic**
272 *Insufficiency*).

273 **ADVERSE REACTIONS**

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

276 *Central Nervous System:* confusion, depression, dysarthria, headache, slurred
277 speech, tremor, vertigo

278 *Gastrointestinal System:* constipation, nausea, gastrointestinal disturbances

279 *Special Senses:* blurred vision, diplopia, dizziness

280 *Cardiovascular System:* hypotension

281 *Psychiatric and Paradoxical Reactions:* stimulation, restlessness, acute
282 hyperexcited states, anxiety, agitation, aggressiveness, irritability, rage,
283 hallucinations, psychoses, delusions, increased muscle spasticity, insomnia,
284 sleep disturbances, and nightmares. Inappropriate behavior and other adverse
285 behavioral effects have been reported when using benzodiazepines. Should
286 these occur, use of the drug should be discontinued. They are more likely to
287 occur in children and in the elderly.

288 *Urogenital System:* incontinence, changes in libido, urinary retention

289 *Skin and Appendages:* skin reactions

290 *Laboratories:* elevated transaminases and alkaline phosphatase

291 *Other:* changes in salivation, including dry mouth, hypersalivation

292 Antegrade amnesia may occur using therapeutic dosages, the risk increasing at
293 higher dosages. Amnestic effects may be associated with inappropriate
294 behavior.

295 Minor changes in EEG patterns, usually low-voltage fast activity, have been
296 observed in patients during and after Valium therapy and are of no known
297 significance.

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

300 **DRUG ABUSE AND DEPENDENCE**

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

309 Withdrawal symptoms, similar in character to those noted with barbiturates
310 and alcohol have occurred following abrupt discontinuance of diazepam.
311 These withdrawal symptoms may consist of tremor, abdominal and muscle
312 cramps, vomiting, sweating, headache, muscle pain, extreme anxiety, tension,
313 restlessness, confusion and irritability. In severe cases, the following
314 symptoms may occur: derealization, depersonalization, hyperacusis,
315 numbness and tingling of the extremities, hypersensitivity to light, noise and
316 physical contact, hallucinations or epileptic seizures. The more severe
317 withdrawal symptoms have usually been limited to those patients who had
318 received excessive doses over an extended period of time. Generally milder
319 withdrawal symptoms (e.g., dysphoria and insomnia) have been reported
320 following abrupt discontinuance of benzodiazepines taken continuously at
321 therapeutic levels for several months. Consequently, after extended therapy,
322 abrupt discontinuation should generally be avoided and a gradual dosage
323 tapering schedule followed.

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

327 ***Rebound Anxiety:*** A transient syndrome whereby the symptoms that led to
328 treatment with Valium recur in an enhanced form. This may occur upon
329 discontinuation of treatment. It may be accompanied by other reactions
330 including mood changes, anxiety, and restlessness.

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

334 **OVERDOSAGE**

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

342 **Management of Overdosage**

343 Following overdose with oral benzodiazepines, general supportive measures
344 should be employed including the monitoring of respiration, pulse, and blood
345 pressure. Vomiting should be induced (within 1 hour) if the patient is
346 conscious. Gastric lavage should be undertaken with the airway protected if
347 the patient is unconscious. Intravenous fluids should be administered. If there
348 is no advantage in emptying the stomach, activated charcoal should be given
349 to reduce absorption. Special attention should be paid to respiratory and
350 cardiac function in intensive care. General supportive measures should be
351 employed, along with intravenous fluids, and an adequate airway maintained.
352 Should hypotension develop, treatment may include intravenous fluid therapy,
353 repositioning, judicious use of vasopressors appropriate to the clinical
354 situation, if indicated, and other appropriate countermeasures. Dialysis is of
355 limited value.

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

358 Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the
359 complete or partial reversal of the sedative effects of benzodiazepines and
360 may be used in situations when an overdose with a benzodiazepine is known
361 or suspected. Prior to the administration of flumazenil, necessary measures
362 should be instituted to secure airway, ventilation and intravenous access.
363 Flumazenil is intended as an adjunct to, not as a substitute for, proper
364 management of benzodiazepine overdose. Patients treated with flumazenil
365 should be monitored for re sedation, respiratory depression and other residual
366 benzodiazepine effects for an appropriate period after treatment. **The**
367 **prescriber should be aware of a risk of seizure in association with**
368 **flumazenil treatment, particularly in long-term benzodiazepine users and**
369 **in cyclic antidepressant overdose.** Caution should be observed in the use of
370 flumazenil in epileptic patients treated with benzodiazepines. The complete
371 flumazenil package insert, including **CONTRAINDICATIONS,**
372 **WARNINGS,** and **PRECAUTIONS,** should be consulted prior to use.

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

376 **DOSAGE AND ADMINISTRATION**

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

ADULTS:

USUAL DAILY DOSE:

<i>Management of Anxiety Disorders and Relief of Symptoms of Anxiety.</i>	Depending upon 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 2.5 mg, 1 or 2 times daily initially; increase gradually as needed and tolerated

PEDIATRIC PATIENTS:

Because of varied responses to CNS-acting drugs, initiate therapy with lowest dose and increase as required. Not for use in pediatric patients under 6 months. 1 mg to 2.5 mg, 3 or 4 times daily initially; increase gradually as needed and tolerated

381 **HOW SUPPLIED**

382 For oral administration, Valium is supplied as round, flat-faced scored tablets
383 with V-shaped perforation and beveled edges. Valium is available as follows:
384 2 mg, white - bottles of 100 (NDC 0140-0004-01); 5 mg, yellow - bottles of
385 100 (NDC 0140-0005-01) and 500 (NDC 0140-0005-14); 10 mg, blue -
386 bottles of 100 (NDC 0140-0006-01) and 500 (NDC 0140-0006-14).

387 Engraved on tablets:

388 2 mg—2 VALIUM[®] (front)
389 ROCHE (twice on scored side)

390 5 mg—5 VALIUM[®] (front)
391 ROCHE (twice on scored side)

392 10 mg—10 VALIUM[®] (front)
393 ROCHE (twice on scored side)

394 **STORAGE**

395 Store at room temperature 59° to 86°F (15° to 30°C). Dispense in tight, light-
396 resistant containers as defined in USP/NF.

397 Distributed by:



Pharmaceuticals

398

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