

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VALIUM safely and effectively. See full prescribing information for VALIUM.

VALIUM (diazepam) tablets, for oral use, C-IV
Initial U.S. Approval: 1963

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS; ABUSE, MISUSE, AND ADDICTION; and DEPENDENCE AND WITHDRAWAL REACTIONS
See full prescribing information for complete boxed warning.

- Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation. (5.1, 7.1)
- The use of benzodiazepines, including VALIUM, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Before prescribing VALIUM and throughout treatment, assess each patient's risk for abuse, misuse, and addiction. (5.2)
- Abrupt discontinuation or rapid dosage reduction of VALIUM after continued use may precipitate acute withdrawal reactions, which can be life-threatening. To reduce the risk of withdrawal reactions, use a gradual taper to discontinue VALIUM or reduce the dosage. (2.3, 5.3)

INDICATIONS AND USAGE

VALIUM is a benzodiazepine indicated for the: (1)

- Treatment of anxiety disorders
- Short-term treatment of anxiety symptoms
- Treatment of tremor, acute agitation, hallucinosis, and impending delirium tremens or delirium tremens in acute alcohol withdrawal
- Adjunctive treatment of skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, or stiff-person syndrome
- Adjunctive treatment of seizure disorders

Limitations of Use

- The effectiveness of VALIUM for long-term use (greater than 4 months) has not been evaluated (1)
- VALIUM is not recommended as maintenance monotherapy for the treatment of seizure disorders (1)

DOSAGE AND ADMINISTRATION

- Recommended oral dosage in adults less than 65 years of age: (2.1)

Indication	Recommended Oral Dosage
Treatment of anxiety disorders	2 mg to 10 mg, two to four times daily
Short-term treatment of anxiety symptoms	2 mg to 10 mg, two to four times daily
Treatment of acute alcohol withdrawal*	10 mg, three to four times during the first 24 hours; after 24 hours reduce to 5 mg, three to four times daily, as needed Recommended dosage is intended for most patients. Based on severity of symptoms some patients may require higher dosages. In such cases, increase dosage gradually.
Adjunctive treatment of skeletal muscle spasm*	2 mg to 10 mg, three to four times daily

Adjunctive treatment of seizure disorders	2 mg to 10 mg, two to four times daily
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*See full prescribing information for complete indication (1)

- See full prescribing information for recommended oral dosage in pediatric patients 6 months of age and older, geriatric or debilitated patients, and patients with hepatic impairment (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 2 mg, 5 mg, 10 mg (3)

CONTRAINDICATIONS

- Known hypersensitivity to diazepam or any excipients of VALIUM (4)
- Acute narrow-angle glaucoma (4)

WARNINGS AND PRECAUTIONS

- *Central Nervous System (CNS) Depression:* Caution patients against engaging in hazardous occupations or activities requiring complete mental alertness (e.g., operating machinery or driving a motor vehicle). Avoid alcohol and use other medications that produce CNS depression with caution (5.4, 7.2)
- *Suicidal Behavior and Ideation:* Monitor for suicidal thoughts or behavior (5.5)
- *Worsening of Preexisting Depression:* Monitor for worsening of preexisting depression (5.6)
- *Paradoxical Reactions:* Gradually discontinue VALIUM if paradoxical reactions occur (5.7)
- *Respiratory Depression and Apnea:* Use with caution in patients with impaired respiratory function related to concurrent disease process. Consider discontinuing VALIUM if signs and symptoms of respiratory depression or apnea occur in any patient (5.8)
- *Glaucoma:* Can increase intraocular pressure in patients with glaucoma. May be used in patients with open-angle glaucoma only if receiving appropriate therapy (4, 5.9)
- *Neonatal Sedation and Withdrawal Syndrome:* VALIUM use during pregnancy can result in neonatal sedation and/or neonatal withdrawal syndrome. (5.10, 8.1)

ADVERSE REACTIONS

Most common adverse reactions are drowsiness, fatigue, muscle weakness, and ataxia (6)

To report SUSPECTED ADVERSE REACTIONS, contact Waylis at 1-303-557-7642 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- *CYP3A4 and CYP2C19 Inhibitors:* Based on tolerability, consider reducing dosage of VALIUM. Avoid food or drink containing grapefruit (7.3)
- *CYP3A4 and CYP2C19 Inducers:* Based on clinical response, consider increasing dosage of VALIUM (7.3)

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* Based on animal data, may cause fetal harm (8.1)
- *Pediatric Use:* Not recommended in pediatric patients less than 6 months of age (8.4)
- *Hepatic Impairment:* Patients with hepatic impairment are more sensitive to adverse reactions of VALIUM (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2026

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FULL PRESCRIBING INFORMATION

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS; ABUSE, MISUSE, AND ADDICTION; and DEPENDENCE AND WITHDRAWAL REACTIONS

- Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation [*see Warnings and Precautions (5.1), Drug Interactions (7.1)*].
- The use of benzodiazepines, including VALIUM, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes. Before prescribing VALIUM and throughout treatment, assess each patient's risk for abuse, misuse, and addiction [*see Warnings and Precautions (5.2)*].
- The continued use of benzodiazepines, including VALIUM, may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and higher daily dose. Abrupt discontinuation or rapid dosage reduction of VALIUM after continued use may precipitate acute withdrawal reactions, which can be life-threatening. To reduce the risk of withdrawal reactions, use a gradual taper to discontinue VALIUM or reduce the dosage [*see Dosage and Administration (2.3), Warnings and Precautions (5.3)*].

1 INDICATIONS AND USAGE

VALIUM is indicated for the:

- Treatment of anxiety disorders
- Short-term treatment of anxiety symptoms
- Treatment of tremor, acute agitation, hallucinosis, and impending delirium tremens or delirium tremens in acute alcohol withdrawal
- Adjunctive treatment of skeletal muscle spasm due to:
 - o reflex spasm to local pathology
 - o spasticity caused by upper motor neuron disorders
 - o athetosis
 - o stiff-person syndrome
- Adjunctive treatment of seizure disorders

Limitations of Use

- The effectiveness of VALIUM for long-term use (greater than 4 months) has not been evaluated.
- VALIUM is not recommended as maintenance monotherapy for the treatment of seizure disorders.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage in Adults Less Than 65 Years of Age

Table 1 provides the recommended oral dosage of VALIUM by indication for adults less than 65 years of age.

Table 1: Recommended Dosage in Adults Less than 65 Years of Age

Indication	Recommended Oral Dosage
Treatment of anxiety disorders	2 mg to 10 mg, two to four times daily
Short-term treatment of anxiety symptoms	2 mg to 10 mg, two to four times daily
Treatment of acute alcohol withdrawal*	10 mg, three to four times during the first 24 hours; after 24 hours reduce dosage to 5 mg, three to four times daily, as needed. The recommended dosage is intended for most patients. However, based on severity of symptoms, some patients may require higher dosages. In such cases, increase the dosage gradually, as needed and tolerated, to reduce the risk of adverse reactions.
Adjunctive treatment of skeletal muscle spasm*	2 mg to 10 mg, three to four times daily
Adjunctive treatment of seizure disorders	2 mg to 10 mg, two to four times daily

**[see Indications and Usage (1) for the complete indication]*

2.2 Recommended Dosage in Specific Populations

Pediatric Patients 6 Months of Age and Older

The recommended starting dosage in pediatric patients 6 months of age and older is 1 mg to 2.5 mg orally, three or four times daily. Increase the dosage gradually as needed and tolerated *[see Use in Specific Populations (8.4)]*.

Geriatric or Debilitated Patients

The recommended starting dosage in geriatric patients 65 years of age and older or debilitated patients is 2 mg to 2.5 mg orally, once or twice daily. Increase the dosage gradually as needed and tolerated *[see Use in Specific Populations (8.5, 8.8)]*.

Patients with Hepatic Impairment

In patients with mild or moderate hepatic impairment, reduce the recommended dosage by half compared to those with normal hepatic function *[see Dosage and Administration (2.1)]*. VALIUM is not recommended in patients with severe hepatic impairment *[see Use in Specific Populations (8.6)]*.

2.3 Discontinuation or Dosage Reduction of VALIUM

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue VALIUM or reduce the dosage. If a patient develops withdrawal reactions, consider pausing the taper or increasing the dosage to the previous tapered dosage level. Subsequently decrease the dosage more slowly *[see Warnings and Precautions (5.3), Drug Abuse and Dependence (9.3)]*.

3 DOSAGE FORMS AND STRENGTHS

VALIUM tablets are round, flat-faced and scored with a V-shaped perforation and beveled edges:

- 2 mg: white, engraved with 2 and VALIUM® on the outside edge and vertically scored on reverse side
- 5 mg: yellow, engraved with 5 and VALIUM® on the outside edge and vertically scored on reverse side
- 10 mg: blue, engraved with 10 and VALIUM® on the outside edge and vertically scored on reverse side

4 CONTRAINDICATIONS

VALIUM is contraindicated in patients with:

- Known hypersensitivity to diazepam or any of the excipients of VALIUM
- Acute narrow-angle glaucoma [*see Warnings and Precautions (5.9)*]

5 WARNINGS AND PRECAUTIONS

5.1 Risks from Concomitant Use with Opioids

Concomitant use of benzodiazepines, including VALIUM, and opioids may result in profound sedation, respiratory depression, coma, and death [*see Drug Interactions (7.1)*]. Because of these risks, reserve concomitant prescribing of these drugs in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe VALIUM concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. In patients already receiving an opioid analgesic, prescribe a lower initial dose of VALIUM than indicated in the absence of an opioid and titrate based on clinical response. If an opioid is initiated in a patient already taking VALIUM, prescribe a lower initial dose of the opioid and titrate based upon clinical response.

Advise both patients and caregivers about the risks of respiratory depression and sedation when VALIUM is used with opioids.

5.2 Abuse, Misuse, and Addiction

The use of benzodiazepines, including VALIUM, exposes users to the risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines often (but not always) involve the use of doses greater than the maximum recommended dosage and commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes, including respiratory depression, overdose, or death [*see Drug Abuse and Dependence (9.2)*].

Before prescribing VALIUM and throughout treatment, assess each patient's risk for abuse, misuse, and addiction (e.g., using a standardized screening tool). Use of VALIUM, particularly in patients at elevated risk, necessitates counseling about the risks and proper use of VALIUM along with monitoring for signs and symptoms of abuse, misuse, and addiction. Prescribe the lowest effective dosage; avoid or minimize concomitant use of CNS depressants and other substances associated with abuse, misuse, and addiction (e.g., opioid analgesics, stimulants); and advise patients on the proper disposal of unused drug. If a substance use disorder is suspected, evaluate the patient and institute (or refer them for) early treatment, as appropriate.

5.3 Dependence and Withdrawal Reactions

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue VALIUM or reduce the dosage (a patient-specific plan should be used to taper the dose) [*see Dosage and Administration (2.3)*].

Patients at an increased risk of withdrawal adverse reactions after benzodiazepine discontinuation or rapid dosage reduction include those who take higher dosages, and those who have had longer durations of use.

Acute Withdrawal Reactions

The continued use of benzodiazepines, including VALIUM, may lead to clinically significant physical dependence. Abrupt discontinuation or rapid dosage reduction of VALIUM after continued use, or administration of flumazenil (a benzodiazepine antagonist) may precipitate acute withdrawal reactions, which can be life-threatening (e.g., seizures) [*see Drug Abuse and Dependence (9.3)*].

Protracted Withdrawal Syndrome

In some cases, benzodiazepine users have developed a protracted withdrawal syndrome with withdrawal symptoms lasting weeks to more than 12 months [*see Drug Abuse and Dependence (9.3)*].

5.4 Central Nervous System Depression

Benzodiazepines, including VALIUM, may produce central nervous system (CNS) depression. Caution patients receiving VALIUM against engaging in hazardous occupations or activities requiring complete mental alertness (e.g., operating machinery or driving a motor vehicle). Alcohol should be avoided and medications that produce CNS depression should be used with caution during treatment with VALIUM [*Drug Interactions (7.2)*].

5.5 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including VALIUM, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed.

Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

Table 2: Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Differences: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing VALIUM or any other AED must balance the risk of suicidal thoughts or behaviors with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

5.6 Worsening of Preexisting Depression

Benzodiazepines, including VALIUM, may worsen preexisting depression [see *Warnings and Precautions* (5.5)]. Monitor patients for worsening of preexisting depression. Appropriate precautions (e.g., limiting the total prescription size) should be considered.

5.7 Paradoxical Reactions

Paradoxical reactions, such as aggression, agitation, anger, irritability, psychoses, hallucinations, anxiety, nightmares, and increased muscle spasticity have been reported during benzodiazepine use [see *Adverse Reactions* (6)]. These reactions are more likely to occur in pediatric and geriatric patients. Gradually discontinue VALIUM if paradoxical reactions occur [see *Dosage and Administration* (2.3)].

5.8 Respiratory Depression and Apnea

Use of benzodiazepines, including VALIUM, either alone or in combination with other CNS depressants, may lead to potentially fatal respiratory depression [see *Warnings and Precautions* (5.4)]. In patients with impaired respiratory function treated with benzodiazepines, respiratory depression and apnea have been reported.

Use VALIUM with caution in patients with impaired respiratory function related to a concurrent disease process [see *Use in Specific Populations* (8.7)]. If signs and symptoms of respiratory depression or apnea occur in any patient, consider discontinuing VALIUM.

5.9 Glaucoma

Benzodiazepines, including VALIUM, can increase intraocular pressure in patients with glaucoma. VALIUM may be used in patients with open-angle glaucoma only if they are receiving appropriate therapy. VALIUM is contraindicated in patients with acute narrow-angle glaucoma.

5.10 Neonatal Sedation and Withdrawal Syndrome

Maternal use of VALIUM late in pregnancy can result in sedation (respiratory depression, lethargy, hypotonia) and/or withdrawal symptoms (hyperreflexia, irritability, restlessness, tremors, inconsolable crying, and feeding

difficulties) in the neonate. Monitor neonates exposed to diazepam during pregnancy or labor for signs of sedation and monitor neonates exposed to diazepam during pregnancy for signs of withdrawal; manage these neonates accordingly [see *Use in Specific Populations* (8.1)].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Risks from Concomitant Use with Opioids [see *Warnings and Precautions* (5.1)]
- Abuse, Misuse, and Addiction [see *Warnings and Precautions* (5.2)]
- Dependence and Withdrawal Reactions [see *Warnings and Precautions* (5.3)]
- Central Nervous System Depression [see *Warnings and Precautions* (5.4)]
- Suicidal Behavior and Ideation [see *Warnings and Precautions* (5.5)]
- Worsening of Preexisting Depression [see *Warnings and Precautions* (5.6)]
- Paradoxical Reactions [see *Warnings and Precautions* (5.7)]
- Respiratory Depression and Apnea [see *Warnings and Precautions* (5.8)]
- Glaucoma [see *Warnings and Precautions* (5.9)]
- Neonatal Sedation and Withdrawal Syndrome [see *Warnings and Precautions* (5.10)]

The following adverse reactions associated with the use of VALIUM were identified in clinical studies or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions most commonly reported were drowsiness, fatigue, muscle weakness, and ataxia.

The following adverse reactions have also been reported:

Blood and lymphatic disorders: neutropenia

Eye disorders: blurred vision, diplopia

Gastrointestinal disorders: changes in salivation, including dry mouth and hypersalivation, gastrointestinal disturbances, constipation, nausea

Hepatobiliary disorders: jaundice

Injury, poisoning and procedural complications: falls and fractures. The risk is increased in those taking concomitant CNS depressants (including alcohol) and in geriatric patients.

Investigations: elevated transaminases and alkaline phosphatase

Nervous system disorders: vertigo, dizziness, dysarthria, tremor, headache

Changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during and after VALIUM therapy.

Psychiatric disorders: disorientation, confusional state, decreased alertness, inappropriate behavior, emotional and mood disturbances, depression, acute hyperexcited states, hyperactivity, restlessness, stimulation, anxiety,

nervousness, aggressiveness, agitation, anger, hostility, irritability, psychoses, delusions, hallucinations, insomnia, sleep disturbances, abnormal dreams, nightmares

Anterograde amnesia has been reported, with the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behavior.

Skin and subcutaneous tissue disorders: skin reactions

Urogenital disorders: incontinence, changes in libido, urinary retention

Vascular disorders: hypotension

7 **Drug Interactions**

7.1 Effect of Concomitant Use of Benzodiazepines and Opioids

Limit dosage and duration of concomitant use of VALIUM and opioids and monitor patients closely for respiratory depression and sedation.

The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at gamma-aminobutyric acid (GABAA) sites and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists [see *Warnings and Precautions (5.1)*].

7.2 CNS Depressants and Alcohol

Avoid consumption of alcohol and use caution during concomitant use of other medications that produce CNS depression with VALIUM.

VALIUM produces additive CNS depressant effects, which can include potentially fatal respiratory depression, when used concomitantly with other medications that produce CNS depression, or with consumption of alcohol [see *Warnings and Precautions (5.4, 5.8)*].

7.3 Effects of Other Drugs on VALIUM

Table 3 describes drug interactions where concomitant use of another drug affects VALIUM.

Table 3: Concomitant Use of Other Drugs That Affect VALIUM

CYP3A4 or CYP2C19 Inhibitors¹	
<i>Prevention or Management</i>	Based on tolerability, consider reducing the dosage of VALIUM during concomitant use with CYP3A4 or CYP2C19 inhibitors. Avoid food or drink containing grapefruit juice during treatment with VALIUM.
<i>Mechanism and Clinical Effect(s)</i>	Concomitant use of CYP3A4 or CYP2C19 inhibitors with VALIUM increases the exposure of VALIUM and may lead to increased and prolonged sedation.
CYP3A4 or CYP2C19 Inducers¹	
<i>Prevention or Management</i>	Based on clinical response, consider increasing the dosage of VALIUM during concomitant use with CYP3A4 or CYP2C19 inducers.

<i>Mechanism and Clinical Effect(s)</i>	Concomitant use of VALIUM with CYP3A4 or CYP2C19 inducers may decrease the exposure of VALIUM and lead to decreased efficacy.
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¹See www.fda.gov/CYPandTransporterInteractingDrugs for examples of CYP3A4 and CYP2C19 inhibitors and inducers.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registries

There are pregnancy exposure registries that monitor pregnancy outcomes in women exposed to psychiatric medications and antiepileptic drugs (AEDs), including VALIUM, during pregnancy. Healthcare providers are encouraged to advise patients to register by contacting the appropriate registry below:

- The National Pregnancy Registry for Psychiatric Medications by calling 1-866-961-2388 or visiting online at <https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/othermedications/>.
- The North American Antiepileptic Drug (NAAED) Pregnancy Registry by calling 1-888-233-2334 or online at <http://www.aedpregnancyregistry.org/>.

Risk Summary

Neonates born to mothers using benzodiazepines late in pregnancy have been reported to experience symptoms of sedation and/or neonatal withdrawal [*see Warnings and Precautions (5.10) and Clinical Considerations*]. Available data from published observational studies of pregnant women exposed to benzodiazepines do not support a clear association with benzodiazepines and major birth defects (*see Data*). There are risks to the mother and fetus associated with untreated epilepsy during pregnancy (*see Clinical Considerations*).

In animal studies, administration of diazepam during the organogenesis period of pregnancy resulted in increased incidences of fetal malformations at doses greater than those used clinically. Data for diazepam and other benzodiazepines suggest the possibility of increased neuronal cell death and long-term effects on neurobehavioral and immunological function based on findings in animals following prenatal or early postnatal exposure at clinically relevant doses (*see Data*).

The background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated risk of major birth defects and of miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryo/fetal Risk

Epilepsy, with or without exposure to antiepileptic drugs, has been associated with several adverse outcomes during pregnancy, including preeclampsia, preterm labor, antepartum and postpartum hemorrhage, placental abruption, poor fetal growth, prematurity, fetal death, and maternal mortality. The risk of maternal or fetal injury may be greatest for patients with untreated or poorly controlled convulsive seizures. Females with epilepsy should not discontinue diazepam abruptly due to the risk of status epilepticus or severe seizures, which may be life-threatening [*see Warnings and Precautions (5.3)*].

Fetal/Neonatal Adverse Reactions

Benzodiazepines cross the placenta and may produce respiratory depression, hypotonia, and sedation in neonates. Monitor neonates exposed to VALIUM during pregnancy or labor for signs of sedation, respiratory

depression, hypotonia, and feeding problems. Monitor neonates exposed to VALIUM during pregnancy for signs of withdrawal. Manage these neonates accordingly [see *Warnings and Precautions* (5.10)].

Data

Human Data

Published data from observational studies on the use of benzodiazepines during pregnancy do not report a clear association with benzodiazepines and major birth defects. Although early studies reported an increased risk of congenital malformations with diazepam and chlordiazepoxide, there was no consistent pattern noted. In addition, recent case-control and cohort studies of benzodiazepine use during pregnancy were adjusted for confounding exposures to alcohol, tobacco and other medications; these studies did not support an association with benzodiazepines and major birth defects.

Animal Data

Diazepam has been shown to cause malformations when administered orally to pregnant mice and hamsters during the period of organogenesis at doses of 100 mg/kg/day or greater, approximately 12 and 20 times the maximum recommended human dose (MRHD) based on mg/m² body surface area, respectively. Cleft palate and encephalopathy were the most common and consistently reported malformations produced at maternally toxic doses of diazepam. Rodent studies have indicated that prenatal exposure to diazepam doses similar to those used clinically can produce long-term changes in cellular immune responses, brain neurochemistry, and behavior.

In published animal studies, administration of benzodiazepines or other drugs that enhance GABAergic inhibition to neonatal rats has been reported to result in widespread apoptotic neurodegeneration in the developing brain at clinically relevant plasma concentrations. The window of vulnerability to these changes in rats (postnatal days 0-14) includes a period of brain development that takes place during the third trimester of pregnancy in humans.

8.2 Lactation

Risk Summary

Diazepam and its active metabolite, N-methyldiazepam, are present in breastmilk. There are reports of sedation, poor feeding and poor weight gain in infants exposed to benzodiazepines through breast milk (*see Clinical Considerations*). There are no data on the effects of diazepam and/or its active metabolite on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VALIUM and any potential adverse effects on the breastfed infant from VALIUM or from the underlying maternal condition.

Clinical Considerations

Infants exposed to VALIUM through breastmilk should be monitored for sedation, poor feeding, and poor weight gain.

8.4 Pediatric Use

VALIUM is indicated for use in pediatric patients for the:

- Treatment of anxiety disorders
- Short-term treatment of anxiety symptoms

- Treatment of tremor, acute agitation, hallucinosis, and impending delirium tremens or delirium tremens in acute alcohol withdrawal
- Adjunctive treatment of skeletal muscle spasm due to:
 - o reflex spasm to local pathology
 - o spasticity caused by upper motor neuron disorders
 - o athetosis
 - o stiff-person syndrome
- Adjunctive treatment of seizure disorders

Paradoxical reactions are more likely to occur in pediatric patients than in adult patients [*see Warnings and Precautions (5.7)*].

VALIUM is not recommended for use in pediatric patients less than 6 months of age.

Prolonged central nervous system depression has been observed in neonates treated with diazepam.

8.5 Geriatric Use

Extensive accumulation of diazepam and its major metabolite, des-methyldiazepam, has been noted following chronic administration of diazepam in healthy geriatric male subjects [*see Clinical Pharmacology (12.3)*]. Metabolites of VALIUM are substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function than in patients with normal renal function.

Because geriatric patients are more likely to have decreased renal function, care should be taken in dosage selection. A lower starting dosage is recommended, and the dosage should be increased gradually as needed and tolerated, to reduce the risk of adverse reactions [*see Dosage and Administration (2.2)*].

Paradoxical reactions are more likely to occur in geriatric patients compared to younger adult patients [*see Warning and Precautions (5.7)*].

8.6 Hepatic Impairment

Patients with hepatic impairment are more sensitive to adverse reactions associated with VALIUM, including increased susceptibility to sedation and delirium [*Clinical Pharmacology (12.3)*].

The recommended dosage of VALIUM in patients with mild or moderate hepatic impairment is half the recommended dosage as those with normal hepatic function [*see Dosage and Administration (2.2)*]. Valium is not recommended in patients with severe hepatic impairment.

8.7 Impaired Respiratory Function

In patients with impaired respiratory function, respiratory depression and apnea have been reported with use of benzodiazepines. Use VALIUM with caution in patients with impaired respiratory function related to a concurrent disease process. If signs and symptoms of respiratory depression or apnea occur, consider discontinuing VALIUM [*Warnings and Precautions (5.8)*].

8.8 Debilitated Patients

Debilitated patients are at an increased risk of adverse reactions to VALIUM. A lower starting dosage is recommended, and the dosage should be increased gradually as needed and tolerated, to reduce the risks of adverse reactions [*see Dosage and Administration (2.2)*].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

VALIUM contains diazepam, a Schedule IV controlled substance.

9.2 Abuse

VALIUM is a benzodiazepine and a CNS depressant with a potential for abuse and addiction. Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence. Even taking benzodiazepines as prescribed may put patients at risk for abuse and misuse of their medication. Abuse and misuse of benzodiazepines may lead to addiction.

Abuse and misuse of benzodiazepines often (but not always) involve the use of doses greater than the maximum recommended dosage and commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes, including respiratory depression, overdose, or death. Benzodiazepines are often sought by individuals who abuse drugs and other substances, and by individuals with addictive disorders [*see Warnings and Precautions (5.2)*].

The following adverse reactions have occurred with benzodiazepine abuse and/or misuse: abdominal pain, amnesia, anorexia, anxiety, aggression, ataxia, blurred vision, confusion, depression, disinhibition, disorientation, dizziness, euphoria, impaired concentration and memory, indigestion, irritability, muscle pain, slurred speech, tremors, and vertigo.

The following severe adverse reactions have occurred with benzodiazepine abuse and/or misuse: delirium, paranoia, suicidal ideation and behavior, seizures, coma, breathing difficulty, and death. Death is more often associated with polysubstance use (especially benzodiazepines with other CNS depressants such as opioids and alcohol).

9.3 Dependence

Physical Dependence

VALIUM may produce physical dependence from continued therapy. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Abrupt discontinuation or rapid dosage reduction of benzodiazepines or administration of flumazenil, a benzodiazepine antagonist, may precipitate acute withdrawal reactions, including seizures, which can be life-threatening. Patients at an increased risk of withdrawal adverse reactions after benzodiazepine discontinuation or rapid dosage reduction include those who take higher dosages (i.e., higher and/or more frequent doses) and those who have had longer durations of use [*see Warnings and Precautions (5.3)*].

To reduce the risk of withdrawal reactions, use a gradual taper to discontinue VALIUM or reduce the dosage [*see Dosage and Administration (2.3), Warnings and Precautions (5.3)*].

Acute Withdrawal Signs and Symptoms

Acute withdrawal signs and symptoms associated with benzodiazepines have included abnormal involuntary movements, anxiety, blurred vision, depersonalization, depression, derealization, dizziness, fatigue,

gastrointestinal adverse reactions (e.g., nausea, vomiting, diarrhea, weight loss, decreased appetite), headache, hyperacusis, hypertension, irritability, insomnia, memory impairment, muscle pain and stiffness, panic attacks, photophobia, restlessness, tachycardia, and tremor. More severe acute withdrawal signs and symptoms, including life-threatening reactions, have included catatonia, convulsions, delirium tremens, depression, hallucinations, mania, psychosis, seizures, and suicidality.

Protracted Withdrawal Syndrome

Protracted withdrawal syndrome associated with benzodiazepines is characterized by anxiety, cognitive impairment, depression, insomnia, formication, motor symptoms (e.g., weakness, tremor, muscle twitches), paresthesia, and tinnitus that persists beyond 4 to 6 weeks after initial benzodiazepine withdrawal. Protracted withdrawal symptoms may last weeks to more than 12 months. As a result, there may be difficulty in differentiating withdrawal symptoms from potential re-emergence or continuation of symptoms for which the benzodiazepine was being used.

Tolerance

Tolerance to VALIUM may develop from continued therapy. Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose). Tolerance to the therapeutic effect of VALIUM may develop; however, little tolerance develops to the amnestic reactions and other cognitive impairments caused by benzodiazepines.

10 OVERDOSAGE

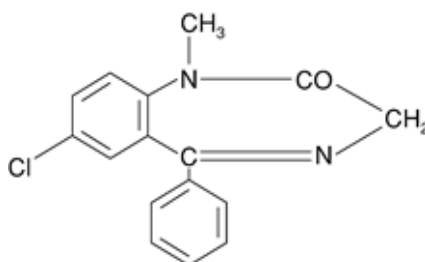
Overdosage of benzodiazepines is characterized by central nervous system depression ranging from drowsiness to coma. In mild to moderate cases, symptoms can include drowsiness, confusion, dysarthria, lethargy, hypnotic state, diminished reflexes, ataxia, and hypotonia. Rarely, paradoxical or disinhibitory reactions (including agitation, irritability, impulsivity, violent behavior, confusion, restlessness, excitement, and talkativeness) may occur. In severe overdosage cases, patients may develop respiratory depression and coma. Overdosage of benzodiazepines in combination with other CNS depressants (including alcohol and opioids) may be fatal [*see Warnings and Precautions (5.2)*]. Markedly abnormal (lowered or elevated) blood pressure, heart rate, or respiratory rate raise the concern that additional drugs and/or alcohol are involved in the overdosage.

In managing benzodiazepine overdosage, employ general supportive measures, including intravenous fluids and airway maintenance. Flumazenil, a specific benzodiazepine receptor antagonist indicated for the complete or partial reversal of the sedative effects of benzodiazepines in the management of benzodiazepine overdosage, can lead to withdrawal and adverse reactions, including seizures, particularly in the context of mixed overdosage with drugs that increase seizure risk (e.g., tricyclic and tetracyclic antidepressants) and in patients with long-term benzodiazepine use and physical dependency. The risk of withdrawal seizures with flumazenil use may be increased in patients with epilepsy. Flumazenil is contraindicated in patients who have received a benzodiazepine for control of a potentially life-threatening condition (e.g., status epilepticus). If the decision is made to use flumazenil, it should be used as an adjunct to, not as a substitute for, supportive management of benzodiazepine overdosage. See the flumazenil injection Prescribing Information.

Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations.

11 DESCRIPTION

VALIUM (diazepam) is a benzodiazepine. 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. Each tablet contains the following inactive ingredients: anhydrous lactose, calcium stearate, corn starch, and pregelatinized starch. The following dyes are also included: 5 mg tablets contain D&C Yellow No. 10 and FD&C Yellow No. 6, and 10 mg tablets contain FD&C Blue No. 1. The 2 mg tablets contain no dye.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of diazepam for the listed indications [*see Indications and Usage (1)*] is thought to involve potentiation of gamma aminobutyric acid (GABA), an inhibitory neurotransmitter, resulting from binding at the benzodiazepine site of the GABA_A receptor.

12.2 Pharmacodynamics

The effects of diazepam on the CNS are dependent on the dose administered, the route of administration, and the presence or absence of other medications.

Diazepam-induced psychomotor impairment in women on contraceptives may be higher during the 7-day menstrual pause when off the hormone preparation than when taking the contraceptive. There is some limited evidence that benzodiazepines can increase the incidence of break-through bleeding in women with hormonal contraceptives.

12.3 Pharmacokinetics

Absorption

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

Following daily dosing, diazepam levels reach a steady state within approximately 5 days and desmethyl diazepam levels reach a steady state within approximately 10 days. Average steady-state levels of diazepam after once daily administration are approximately twice as high as the peak levels of the drug after the first dose.

Effect of Food

Absorption is delayed and decreased when administered with a moderate fat meal. In the presence of food, mean lag times are approximately 45 minutes as compared with 15 minutes when fasting. There is also an increase in the average time to achieve peak concentrations to about 2.5 hours in the presence of food as compared with 1.25 hours when fasting. This results in an average decrease in C_{max} of 20% in addition to a 27% decrease in AUC (range 15% to 50%) when administered with food.

Distribution

Diazepam and its metabolites are highly bound to plasma proteins (diazepam 98%). The volume of distribution at steady-state is 0.8 to 1.0 L/kg. Diazepam and its metabolites cross the blood-brain and placental barriers. The decline in the plasma concentration-time profile after oral administration is biphasic. The initial distribution phase has a half-life of approximately 1 hour, although it may range up to >3 hours.

Both protein binding and volume of distribution of desmethyl-diazepam are similar to those of diazepam.

Elimination

Metabolism

Oxidation of diazepam is mediated by cytochrome P450 isozymes; formation of desmethyl-diazepam mainly by CYP2C19 and CYP3A and 3-hydroxy-diazepam (temazepam) and oxazepam by CYP3A. Diazepam is mainly metabolized to pharmacologically active metabolites such as desmethyl-diazepam, a pathway accounting for 50 to 60% of total diazepam clearance; 3-hydroxylation (27% of total diazepam clearance) is slow, leading to only low plasma levels of the oxidation products temazepam and oxazepam. Temazepam and oxazepam are further conjugated to glucuronides. After multiple doses of diazepam, plasma concentration ratios of desmethyl-diazepam to diazepam were 1.1 ± 0.2 , temazepam to diazepam 0.11 ± 0.05 , and oxazepam to diazepam 0.09 ± 0.03 .

Diazepam has an initial rapid and extensive distribution phase being 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.

Excretion

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. Diazepam accumulates upon multiple dosing and there is some evidence that the terminal elimination half-life is slightly prolonged.

Specific Populations

Geriatric Patients

Age decreases the capacity of the liver for N-demethylation and 3-hydroxylation of diazepam. Elimination half-life increases by approximately 1 hour for each year of age beginning with a half-life of 20 hours at 20 years of age. This appears to be due to an increase in volume of distribution with age and a decrease in clearance. Consequently, geriatric patients may have lower peak concentrations, and on multiple dosing higher trough concentrations. It will also take longer to reach steady-state [see *Dosage and Administration* (2.2), *Use in Specific Populations* (8.5)]. Conflicting information has been published on changes of plasma protein binding in geriatric patients.

Pediatric Patients

In pediatric patients 3 to 8 years of age the mean half-life of diazepam has been reported to be 18 hours [see *Dosage and Administration* (2.2)].

Patients with Renal Impairment

In chronic renal failure, elimination of diazepam, as indicated by clearance of unbound drug, was similar to that in healthy volunteers; thus steady-state concentrations of unbound diazepam at any given daily dose on the average should not be different between patients with renal impairment and healthy individuals.

Patients with Hepatic Impairment

In mild and moderate cirrhosis, average half-life is increased. The average increase has been variously reported from 2-fold to 5-fold, with individual half-lives over 500 hours reported. There is also an increase in volume of distribution, and average clearance decreases by almost half. Mean half-life is also prolonged with hepatic fibrosis to 90 hours (range 66 to 104 hours), with chronic active hepatitis to 60 hours (range 26 to 76 hours), and with acute viral hepatitis to 74 hours (range 49 to 129). In chronic active hepatitis, clearance is decreased by almost half [see *Dosage and Administration* (2.2), *Use in Specific Populations* (8.6)].

Drug Interaction Studies

The metabolism of diazepam and its main metabolite, desmethyl-diazepam depends on the cytochrome P450 isozymes CYP3A4 and CYP2C19. Modulators of these enzymes may lead to changes in diazepam disposition and effects. Inhibitors of CYP3A4 and CYP2C19 decrease metabolic rate and may lead to higher concentrations of diazepam and the desmethyl metabolite. Inducers of CYP3A4 and CYP2C19 may lead to lower concentrations of diazepam and the desmethyl metabolite [see *Drug Interactions (7.3)*].

Effect of Other Drugs on the Pharmacokinetics of Diazepam

Enzyme Inhibitors

Grapefruit juice contains strong inhibitors of CYP3A4. Diazepam exposure was increased and time to reach maximum concentration was delayed when diazepam was given with grapefruit juice instead of water [see *Drug Interactions (7.3)*].

Antimycotic azole derivatives inhibit CYP3A4 and CYP2C19 pathways and lead to increased exposure to diazepam and prolonged elimination half-life of diazepam [see *Drug Interactions (7.3)*].

The serotonin reuptake inhibitor fluvoxamine is also an inhibitor of both of diazepam's degradation pathways and increased not only exposure to diazepam and prolonged its elimination half-life but also increased exposure and time to reach steady-state of the desmethyl metabolite. Fluoxetine showed a more moderate effect on diazepam AUC [see *Drug Interactions (7.3)*].

Combined hormonal contraceptives appear to reduce the clearance and prolong elimination half-life of diazepam.

Proton pump inhibitors such as omeprazole, esomeprazole, lansoprazole, pantoprazole may increase the diazepam AUC.

The histamine H₂-receptor antagonist cimetidine, an inhibitor of multiple CYP isozymes, including CYP3A4 and CYP2C19, reduces the clearance of diazepam and of desmethyl-diazepam and results in higher exposure and a prolonged elimination half-life of diazepam and its main metabolite [see *Drug Interactions (7.3)*]. No such pharmacokinetic interaction was seen with the H₂-receptor antagonists ranitidine and famotidine.

Disulfiram inhibits the metabolism of diazepam and likely the further metabolism of diazepam's active metabolites.

Antituberculosis therapy may change the disposition of diazepam. In the presence of isoniazid, diazepam mean exposure (AUC) and half-life were increased.

The calcium channel blocker diltiazem, a substrate for the same CYP isozymes as diazepam and an inhibitor of CYP3A4, increased AUC and prolonged half-life of diazepam [see *Drug Interactions (7.3)*].

The primary metabolite of idelalisib is a strong CYP3A4 inhibitor and increases the serum concentrations of diazepam [see *Drug Interactions (7.3)*].

The psychostimulants modafinil and armodafinil induce CYP3A4 and inhibit CYP2C19; they may prolong the elimination of diazepam [see *Drug Interactions (7.3)*].

Enzyme Inducers

Rifampicin and carbamazepine, potent inducers of CYP3A4, may lead to a reduction in exposure of diazepam [see *Drug Interactions (7.3)*].

Antacids

Antacids may lower the diazepam peak but have no effect on the extent of absorption of diazepam. Diazepam peak concentrations are 30% lower when antacids are administered concurrently. However, there is no effect on

the extent of absorption. The time to reach peak concentrations are 20-25 min longer for diazepam in presence of antacids.

Effect of Diazepam on the Pharmacokinetics of Other Drugs

Diazepam has not been found to induce or inhibit metabolizing enzymes.

Diazepam is a substrate for CYP2C19 and CYP3A4; therefore, VALIUM may interfere with the metabolism and increase the exposure of drugs which are sensitive substrates for CYP2C19 and CYP3A4.13

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

An increased incidence of liver tumors was observed in male mice and rats that were administered diazepam in the diet for 80 and 104 weeks, respectively at a dose of 75 mg/kg/day, approximately 9 and 18 times the maximum recommended human dose (MRHD) based on mg/m² body surface area, respectively.

Mutagenesis

The data currently available are inadequate to determine the mutagenic potential of diazepam.

Impairment of Fertility

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 24 times the MRHD based on mg/m² body surface area) prior to and during mating and throughout gestation and lactation. No adverse effects on fertility or offspring viability were noted up to a dose of 80 mg/kg/day (approximately 19 times the MRHD based on mg/m² body surface area).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

VALIUM are round, flat-faced scored tablets with a V-shaped perforation and beveled edges and are supplied in bottles of 100 as follows:

Tablet Strength	Color	Engraved Descriptors	NDC Number
2 mg	white	2 and VALIUM® on the outside edge and vertically scored on reverse side	NDC 80725-004-01
5 mg	yellow	5 and VALIUM® on the outside edge and vertically scored on reverse side	NDC 80725-005-01
10 mg	blue	10 and VALIUM® on the outside edge and vertically scored on reverse side	NDC 80725-006-01

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Dispense in tight, light-resistant containers as defined in USP/NF.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Risks from Concomitant Use with Opioids

Advise both patients and caregivers about the risks of potentially fatal respiratory depression and sedation when VALIUM is used with opioids and not to use such drugs concomitantly unless supervised by a healthcare provider [see *Warnings and Precautions* (5.1), *Drug Interactions* (7.1)].

Abuse, Misuse, and Addiction

Inform patients that the use of VALIUM, even at recommended dosages, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose and death, especially when used in combination with other medications (e.g., opioid analgesics), alcohol, and/or illicit substances. Inform patients about the signs and symptoms of benzodiazepine abuse, misuse, and addiction; to seek medical help if they develop these signs and/or symptoms; and on the proper disposal of unused drug [see *Warnings and Precautions* (5.2), *Drug Abuse and Dependence* (9.2)].

Withdrawal Reactions

Inform patients that the continued use of VALIUM may lead to clinically significant physical dependence and that abrupt discontinuation or rapid dosage reduction of VALIUM may precipitate acute withdrawal reactions, which can be life-threatening. Inform patients that in some cases, patients taking benzodiazepines have developed a protracted withdrawal syndrome with withdrawal symptoms lasting weeks to more than 12 months. Instruct patients that discontinuation or dosage reduction of VALIUM may require a slow taper [see *Dosage and Administration* (2.3), *Warnings and Precautions* (5.3), *Drug Abuse and Dependence* (9.3)].

Central Nervous System Depression

Inform patients that VALIUM may produce CNS depression. Advise patients not to engage in hazardous occupations or activities requiring complete mental alertness such as driving a motor vehicle or operating heavy machinery. Also advise patients to avoid use of alcohol while taking VALIUM [see *Warnings and Precautions* (5.4), *Drug Interactions* (7.2)].

Suicidal Behavior and Ideation

Counsel patients, their caregivers, and families that AEDs, including VALIUM, may increase the risk of suicidal thoughts and behavior and advise them of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Advise patients to report behaviors of concern immediately to healthcare providers [see *Warnings and Precautions* (5.5)].

Worsening of Preexisting Depression

Inform patients that VALIUM may worsen preexisting depression. Advise patients to report symptoms of worsening depression to their healthcare provider [see *Warnings and Precautions* (5.6)].

Paradoxical Reactions

Inform patients that paradoxical reactions such as aggression, agitation, anger, irritability, psychoses, hallucinations, anxiety, and nightmares have been reported during benzodiazepine use. Advise patients to contact their healthcare provider if paradoxical reactions occur [*see Warnings and Precautions (5.7)*].

Concomitant Medications

Advise patients to inform their healthcare provider of all medicines they take, including prescription and nonprescription medications, vitamins and herbal supplements [*see Drug Interactions (7)*].

Grapefruit Juice

Advise patients to avoid eating grapefruit or drinking grapefruit juice while taking VALIUM [*see Drug Interactions (7.3)*].

Pregnancy

Advise pregnant women that the use of VALIUM late in pregnancy can result in sedation (respiratory depression, lethargy, hypotonia) and/or withdrawal symptoms (hyperreflexia, irritability, restlessness, tremors, inconsolable crying and feeding difficulties) in newborns [*see Warnings and Precautions (5.10), Use in Specific Populations (8.1)*]. Instruct patients to inform their healthcare providers if they are pregnant or intend to become pregnant during treatment with Valium.

Advise patients that there are pregnancy exposure registries that monitor pregnancy outcomes in women exposed to VALIUM during pregnancy [*see Use in Specific Populations (8.1)*].

Lactation

Counsel patients that diazepam, the active ingredient in VALIUM, is excreted in breast milk. Instruct patients to inform their healthcare provider if they are breastfeeding or intend to breastfeed. Instruct breastfeeding patients who take VALIUM to monitor their infants for excessive sedation, poor feeding and poor weight gain, and to seek medical attention if they notice these signs [*see Use in Specific Populations (8.2)*].

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MEDICATION GUIDE
VALIUM (VAL-ee-um)
(diazepam)
tablets, C-IV

What is the most important information I should know about VALIUM?

VALIUM may cause serious side effects, including:

- **VALIUM is a benzodiazepine medicine. Taking benzodiazepines with opioid medicines, alcohol, or other central nervous system (CNS) depressants (including street drugs) can cause severe drowsiness, breathing problems (respiratory depression), coma and death.** Get emergency help right away if any of the following happens:
 - shallow or slowed breathing,
 - breathing stops (which may lead to the heart stopping),
 - excessive sleepiness (sedation).
- **Risk of abuse, misuse, and addiction.** There is a risk of abuse, misuse, and addiction with benzodiazepines, including VALIUM, which can lead to overdose and serious side effects including coma and death.
 - **Serious side effects including coma and death have happened in people who have abused or misused benzodiazepines, including VALIUM.** These serious side effects may also include delirium, paranoia, suicidal thoughts or actions, seizures, and difficulty breathing. **Call your healthcare provider or go to the nearest hospital emergency room right away if you get any of these serious side effects.**
 - **You can develop an addiction even if you take VALIUM exactly as prescribed by your healthcare provider.**
 - **Take VALIUM exactly as your healthcare provider prescribed.**
 - **Do not** share your VALIUM with other people.
 - Keep VALIUM in a safe place and away from children. Properly dispose of any unused medicine.
- **Physical dependence and withdrawal reactions.** VALIUM can cause physical dependence and withdrawal reactions.
 - **Do not suddenly stop taking VALIUM.** Stopping VALIUM suddenly can cause serious and life-threatening side effects, including, unusual movements, responses, or expressions, seizures, sudden and severe mental or nervous system changes, depression, seeing or hearing things that others do not see or hear, an extreme increase in activity or talking, losing touch with reality, and suicidal thoughts or actions. **Call your healthcare provider or go to the nearest hospital emergency room right away if you get any of these symptoms.**
 - **Some people who suddenly stop benzodiazepines have symptoms that can last for several weeks to more than 12 months,** including, anxiety, trouble remembering, learning, or concentrating, depression, problems sleeping, feeling like insects are crawling under your skin, weakness, shaking, muscle twitching, burning or prickling feeling in your hands, arms, legs or feet, and ringing in your ears.
 - Physical dependence is not the same as drug addiction. Your healthcare provider can tell you more about the differences between physical dependence and drug addiction.
 - **Do not** take more VALIUM than prescribed or take VALIUM for longer than prescribed.
- **VALIUM can make you sleepy or dizzy and can slow your thinking and motor skills.**
 - **Do not** drive, operate heavy machinery, or do other dangerous activities during treatment with VALIUM.
 - **Do not** drink alcohol or take other drugs that may make you sleepy or dizzy during treatment with VALIUM without first talking to your healthcare provider. When taken with alcohol or drugs that cause sleepiness or dizziness, VALIUM may make your sleepiness or dizziness much worse.
- **Suicide actions and thoughts. Like other antiepileptic drugs, VALIUM may cause suicidal thoughts or actions in a very small number of people, about 1 in 500,** including when it is used for other indications besides seizures.

Tell your healthcare provider right away if you get any of these symptoms, especially if they are new, worse, or worry you:

- | | |
|---|---|
| ○ thoughts about suicide or dying | ○ suicide attempts |
| ○ new or worse depression | ○ new or worse anxiety or irritability |
| ○ feeling agitated or restless | ○ an extreme increase in activity and talking (mania) |
| ○ trouble sleeping (insomnia) | ○ new or worse panic attacks |
| ○ acting aggressive, being angry or violent | ○ acting on dangerous impulses |
| ○ other unusual changes in behavior or mood | |

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.

Tell your healthcare provider between visits as needed, especially if you are worried about symptoms. Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

See “What are the possible side effects of VALIUM?” for more information about side effects.

What is VALIUM?

VALIUM is a prescription medicine used:

- to treat anxiety disorders
- short-term to treat anxiety symptoms
- To treat symptoms of suddenly stopping drinking alcohol (acute alcohol withdrawal) which can include shaking (tremor), agitation, seeing or hearing things that others do not see or hear (hallucinations), and sudden and severe mental or nervous system changes (delirium tremens)
- along with other medicines to treat muscle spasms from:
 - injuries or strains
 - certain neurological conditions
 - a movement disorder called athetosis
 - stiff-person syndrome
- along with other medicines to treat seizure disorders

VALIUM is a federal controlled substance (C-IV) because it contains diazepam that can be abused or lead to dependence. Keep VALIUM in a safe place to prevent misuse and abuse. Selling or giving away VALIUM may harm others and is against the law. Tell your healthcare provider if you have abused or been dependent on alcohol, prescription medicines or street drugs.

It is not known if VALIUM is effective for use for longer than 4 months.

VALIUM is not recommended alone as maintenance therapy for the treatment of seizure disorders.

VALIUM is not recommended for use in children less than 6 months of age.

Who should not take VALIUM?

Do not take VALIUM if you:

- are allergic to diazepam or any of the ingredients in VALIUM. See the end of this Medication Guide for a complete list of ingredients in VALIUM.
- have an eye problem called acute narrow-angle glaucoma

Before taking VALIUM, tell your healthcare provider about all of your medical conditions, including if you:

- have a history of drug or alcohol abuse
- have or had depression, mood problems, or suicidal thoughts or behavior
- have lung or breathing problems
- have liver or kidney problems
- are pregnant or plan to become pregnant.
 - Taking VALIUM late in pregnancy can cause your baby to have symptoms of sedation (breathing problems, sluggishness, low muscle tone) and/or withdrawal symptoms (jitteriness, irritability, restlessness, shaking, excessive crying, feeding problems).
 - Tell your healthcare provider right away if you become pregnant or think you are pregnant during treatment with VALIUM.
 - There are pregnancy registries for women who take VALIUM during pregnancy. The purpose of these registries is to collect information about the health of you and your baby. If you become pregnant during treatment with VALIUM, talk to your healthcare provider about registering with the appropriate registry:
 - the National Pregnancy Registry for Psychiatric Medications by calling 1-866-961-2388 or visiting <https://womensmentalhealth.org/researchpregnancyregistry/>.
 - the North American Antiepileptic Drug (NAAED) Pregnancy Registry by calling 1-888-233-2334 or visiting <http://www.aedpregnancyregistry.org/>.
- are breastfeeding or plan to breastfeed. VALIUM passes into your breast milk.
 - Talk to your healthcare provider about the best way to feed your baby during treatment with VALIUM.
 - If you breastfeed during treatment with VALIUM, monitor your baby for excessive sleepiness, poor feeding, and poor weight gain. Get medical help right away if your baby gets any of these symptoms.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking VALIUM with certain other medicines can cause side effects or affect how well VALIUM or the other medicines work. **Do not** start or stop other medicines without talking to your healthcare provider.

How should I take VALIUM?

- Take VALIUM exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much VALIUM to take and when to take it.
- **Do not** stop taking VALIUM without first talking to your healthcare provider. Your healthcare provider will tell you how to slowly stop VALIUM to avoid withdrawal symptoms. See “What is the most important information I should know about VALIUM?”
- If you take too much VALIUM, call your healthcare provider or Poison Help line at 1-800-222-1222 or go to the nearest hospital emergency room right away.

What should I avoid while taking VALIUM?

- See “What are the possible side effects of VALIUM?”
- Avoid eating grapefruit or drinking grapefruit juice during treatment with VALIUM.

What are the possible side effects of VALIUM?

VALIUM may cause serious side effects, including:

- See “What is the most important information I should know about VALIUM?”
- **Worsening of preexisting depression.** Tell your healthcare provider if you get symptoms of worsening depression.
- **Abnormal thoughts and behavior (paradoxical reactions).** Symptoms include aggressive behavior, agitation, anger, irritability, confusion, beliefs that are not true, hallucinations, anxiety, nightmares, and increased muscle stiffness or tightness. These reactions are more likely to happen in children and elderly people. Tell your healthcare provider if you get any of these symptoms.
- **Slowed and stopped breathing** that may lead to death when benzodiazepines, including VALIUM, are taken alone or with certain other medicines. Slowed and stopped breathing has happened in people who have breathing problems and take benzodiazepines like VALIUM. Tell your healthcare provider right away if you get any breathing problems.
- **Increase in eye pressure in people with open-angle glaucoma.** See “Who should not take VALIUM?”

The most common side effects of VALIUM include:

- drowsiness
- tiredness
- muscle weakness
- loss of control of body movements (ataxia)

These are not all the possible side effects of VALIUM.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Waylis at 1-303-557-7642

How should I store VALIUM?

- Store VALIUM at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep VALIUM in a tightly closed container and out of light.

Keep VALIUM and all medicines out of the reach of children.

General information about the safe and effective use of VALIUM.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use VALIUM for a condition for which it was not prescribed. Do not give VALIUM to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about VALIUM that is written for health professionals.

What are the ingredients in VALIUM?

Active ingredient: diazepam

Inactive ingredients: anhydrous lactose, calcium stearate, corn starch, and pregelatinized starch. The following dyes are also included: 5 mg tablets contain D&C Yellow No. 10 and FD&C Yellow No. 6, and 10 mg tablets contain FD&C Blue No. 1. The 2 mg tablets contain no dye.

Distributed by: Waylis Therapeutics LLC., Rahway, NJ 07065
For more information, call 1-303-557-7642.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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