



# PRESCRIBING INFORMATION

## VALIUM® ROCHE®

(diazepam)

Tablets

5 mg, 10 mg

ANXIOLYTIC-SEDATIVE

**HOFFMANN-LA ROCHE LIMITED**  
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## NAME OF DRUG

**VALIUM® ROCHE®**

**(diazepam)**

**Tablets**

**5 mg, 10 mg**

## THERAPEUTIC CLASSIFICATION

**Anxiolytic-sedative**

## ACTIONS AND CLINICAL PHARMACOLOGY

'Valium' (diazepam) is an anxiolytic-sedative drug useful in the symptomatic relief of anxiety and tension states. It has also adjunctive value in the relief of certain neurospastic conditions.

### **ABSORPTION:**

Diazepam is rapidly and completely absorbed from the gastrointestinal tract, peak plasma concentrations appearing 30-90 minutes after oral ingestion.

### **DISTRIBUTION:**

Diazepam and its metabolites are highly bound to plasma proteins (diazepam 98%). The volume of distribution at steady state is 0.8-1.0 L/kg. In humans, comparable blood levels of 'Valium' were obtained in maternal and cord blood indicating placental transfer of the drug.

### **METABOLISM:**

Diazepam is mainly metabolized to the pharmacologically active metabolites such as N-desmethyldiazepam, temazepam and oxazepam.

### **ELIMINATION:**

The acute half-life is six to eight hours with a slower decline thereafter (half-life up to 48 hours). The terminal elimination half-life of the active metabolite N-desmethyldiazepam is up to 100 hours. Diazepam and its metabolites are excreted mainly in the urine, predominantly in their conjugated forms. The clearance of diazepam is 20-30 mL/min.

### **PHARMACOKINETICS IN SPECIAL CLINICAL SITUATIONS :**

The elimination half-life may be prolonged in the newborn, in the elderly and in patients with liver disease. In renal failure the half-life of diazepam is unchanged.

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## INDICATIONS

Benzodiazepines are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

'Valium' (diazepam) is useful in the symptomatic management of mild to moderate degrees of anxiety in conditions dominated by tension, excitation, agitation, fear or aggressiveness, such as may occur in:- psychoneurosis, anxiety reactions due to stress conditions and anxiety states with somatic expression.

In acute alcoholic withdrawal, 'Valium' may be useful in the symptomatic relief of acute agitation, tremor and impending acute delirium tremens.

'Valium' is a useful adjunct for the relief of skeletal muscle spasm due to reflex spasm to local pathology, such as inflammation of the muscle and joints or secondary to trauma; spasticity caused by upper motor neuron disorders, such as cerebral palsy and paraplegia; athetosis and the rare "stiff man syndrome".

## CONTRAINDICATIONS

'Valium' (diazepam) is contraindicated in patients with:

A known hypersensitivity to benzodiazepines, severe respiratory insufficiency, severe hepatic insufficiency, sleep apnea syndrome, myasthenia gravis and, because of lack of sufficient clinical experience, in children under six months of age.

## WARNINGS

'Valium' (diazepam) is not recommended in patients with dependence on other substances including alcohol. An exception to the latter is the management of acute withdrawal reactions.

Benzodiazepines are not recommended for the primary treatment of psychotic illness.

Benzodiazepines should not be used alone to treat depression or anxiety associated with depression as suicide may occur in such patients.

## PRECAUTIONS

Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse.

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

### TOLERANCE:

Some loss of response to the effects of benzodiazepines may develop after repeated use of 'Valium' (diazepam) for prolonged time.

### DEPENDENCE:

Use of benzodiazepines and benzodiazepine-like agents may lead to the development of physical and psychological dependence. This risk of dependence increases with dose and duration of treatment (48,56,57); it is also greater in predisposed patients with a history of alcohol or drug abuse.

**WITHDRAWAL:**

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headache, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases, the following symptoms may occur: derealization, depersonalization, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

**REBOUND ANXIETY:**

A transient syndrome whereby the symptoms that led to treatment with 'Valium' recur in an enhanced form. This may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness.

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

**AMNESIA:**

It should be borne in mind that benzodiazepines may induce anterograde amnesia. Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Effects of this may be associated with inappropriate behaviour.

**PSYCHIATRIC AND 'PARADOXICAL' REACTIONS:**

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines. Should this occur, the use of the drug should be discontinued. They are more likely to occur in children and in the elderly.

**USE IN ELDERLY:**

Elderly and debilitated patients or those with organic brain disorders have been found to be prone to central nervous system depression following even low doses. For these patients it is recommended that the dosage be limited to the smallest, effective amount to preclude development of ataxia, over sedation or other possible adverse effects.

**USE IN EPILEPTIC PATIENT:**

Careful consideration should be given if 'Valium' is to be used in patients with epilepsy as the possibility of an increase in the frequency and/or severity of grand mal seizures may require an increase in the doses of standard anticonvulsant medication. An abrupt withdrawal of 'Valium' in such cases may also be associated with the temporary increase in the frequency and/or severity of seizures.

**USE IN PREGNANCY AND NURSING:**

The safety of diazepam for use in pregnancy has not been established. An increased risk of congenital malformation associated with the use of benzodiazepines during the first trimester of pregnancy has been suggested. 'Valium' Injection should not be used during pregnancy except if absolutely necessary.

Continuous administration of benzodiazepines during pregnancy may give rise to hypotension, reduced respiratory function and hypothermia in the newborn child. Withdrawal symptoms in newborn infants have occasionally been reported with this class of drug. Special care must be taken when 'Valium' is used during labour and delivery, as high single doses may produce irregularities in the fetal heart rate and hypotonia, poor sucking, hypothermia and moderate respiratory depression in the neonate. With newborn infants it must be remembered that the enzyme system involved in the breakdown of the drug is not yet fully developed (especially in premature infants).

Diazepam passes into breast milk. Breast-feeding is therefore not recommended in patients receiving 'Valium'.

**GENERAL:**

Patients receiving 'Valium' should be advised to proceed cautiously wherever mental alertness and physical coordination are required.

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

**DRUG INTERACTIONS :**

Careful consideration should be given if 'Valium' is to be combined with other centrally acting agents, such as (antipsychotics, anxiolytics/sedatives, antidepressants, hypnotics, anticonvulsants, narcotic analgesics, anesthetics and sedative antihistamines because the pharmacological action of these (84) agents might potentiate or be potentiated by the action of 'Valium'. Since 'Valium' has a central nervous system depressant effect, patients should be advised against the simultaneous ingestion of alcohol and other central nervous system depressant drugs during 'Valium' therapy.

There is potentially relevant interaction between diazepam and compounds which inhibit certain hepatic enzymes (particularly cytochrome P 450 III A). Data indicate that these compounds influence the pharmacokinetics of diazepam and may lead to increased and prolonged sedation. At present this reaction is known to occur with cimetidine, ketoconazole, fluvoxamine and fluoxetine and omeprazole.

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

Cisapride may lead to a temporary increase in the sedative effects of orally administered benzodiazepines due to faster absorption.

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## ADVERSE REACTIONS

The most common adverse reactions reported for 'Valium' (diazepam) are fatigue, drowsiness, muscle weakness and ataxia. These phenomena occur predominantly at the start of therapy and usually disappear with prolonged administration.

The following may also occur: dizziness, nausea, dry mouth or hypersalivation, blurred vision, diplopia, headache, slurred speech, tremors, dysarthria, confusion, depression, incontinence or urinary retention, constipation, gastrointestinal disturbances, skin rash, generalized exfoliative dermatitis, hypotension and changes in libido; very rarely, elevated transaminases and alkaline phosphatase have been reported occasionally.

Other reactions noted less frequently are vertigo, hypoactivity, euphoria and impairment of memory.

Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Effects of this be associated with inappropriate behaviour.

The more serious adverse reactions occasionally reported are leucopenia, jaundice and hypersensitivity.

### PSYCHIATRIC AND 'PARADOXICAL' REACTIONS :

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines . Should these occur, the drug should be discontinued. They are more likely to occur in children and in the elderly.

Minor changes in EEG patterns have been observed in patients on. 'Valium' therapy. These changes consist of low to moderate voltage fast activity, 20 to 30 cycles per second and are of no known significance.

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

Abuse of benzodiazepines has been reported.

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## SYMPTOMS AND TREATMENT OF OVERDOSAGE

### SYMPTOMS

The main symptoms of overdosage are drowsiness, over sedation and ataxia. When the effects of the drug overdosage begin to wear off, the patient exhibits some jitteriness and overstimulation. The cardinal manifestations of overdosage are drowsiness and confusion, reduced reflexes and coma (rarely) and death (very rarely). However, overdose should not present a threat to life unless combined with other CNS depressants (including alcohol). There are minimum effects on respiration, pulse and blood pressure unless the overdosage is extreme.

### TREATMENT

In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken.

Vomiting should be induced (within 1 hour) if the patient is conscious or gastric lavage, with the airway protected if the patient is unconscious, may be beneficial if performed soon after oral ingestion of 'Valium' (diazepam). If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. If necessary, a CNS stimulant such as caffeine or methylphenidate may be administered with caution. Supportive measures should be instituted as indicated:- maintenance of an adequate airway, levarterenol or metaraminol bitartrate for hypotension. Flumazenil may be useful as an antagonist. Caution should be observed in the use of flumazenil in epileptics treated with benzodiazepines. Dialysis appears to be of little value.

## DOSAGE AND ADMINISTRATION

Dosage for 'Valium' (diazepam) should be individualized for maximal beneficial effect. While the usual daily dosages given below will meet the needs of most patients, there will be some who may require higher doses. In the first few days of administration a cumulative effect of drug may occur, and therefore, the dosage should be increased only after stabilization is apparent.

### DURATION OF TREATMENT

The duration of treatment should be as short as possible. The patient should be reassessed regularly and the need for continued treatment evaluated, especially if the patient is symptom free. It should not exceed 2- 3 months, including the tapering-off period. Extension beyond this period should not take place without reevaluation of the situation. It may be useful to inform the patient when treatment is started that it will be of limited duration and explain precisely how the dosage will be progressively decreased. Moreover, it is important that the patient be aware of the possibility of rebound phenomena, thereby minimizing anxiety over such symptoms should they occur during withdrawal. There is evidence that, in the case of short-acting benzodiazepines, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high. When long-acting benzodiazepines such as diazepam are being used, it is important to warn against changing to a short-acting benzodiazepine as withdrawal symptoms may develop.

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**USUAL DAILY DOSE****ADULTS:**

Symptomatic relief of anxiety and tension in psychoneurosis and anxiety reactions	Depending upon severity of symptoms - 2 mg to 10 mg, two to four times daily.
Symptomatic relief in acute alcohol withdrawal	10 mg, three or four times during the first 24 hours, reducing to 5 mg, three or four times daily as needed.
Adjunctively for relief of skeletal muscle spasm.	2 mg to 10 mg, three to four times daily.
Elderly and debilitated patients, or in the presence of debilitating disease.	2 mg, one or two times daily initially, increase gradually as needed and tolerated

**CHILDREN:**

Because of varied responses, initiate therapy with lowest dose and increase as required. Not for use in children under six months. (See Contraindications)	1 mg to 2½ mg, three or four times daily initially; increase gradually as needed and tolerated.
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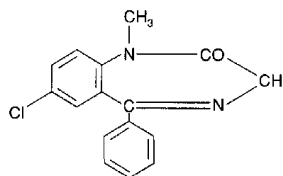
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## PHARMACEUTICAL INFORMATION

### CHEMISTRY

'Valium' contains as active substance diazepam (7-chloro-1, 3-dihydro-1-methyl-5-phenyl-2H-1, 4-benzodiazepine-2-one), a benzodiazepine derivative. It is a colorless, crystalline compound, insoluble in water and has a molecular weight of 284.74.

### STRUCTURAL FORMULA



### COMPOSITION

'Valium' is available for oral administration as tablets containing 5 mg of diazepam. Non-medicinal ingredients are corn starch, iron oxide yellow, lactose and magnesium stearate.

### AVAILABILITY OF DOSAGE FORMS

'Valium' (diazepam) Scored Tablets: 5 mg, yellow; and 10 mg, blue.