Valium®

Diazepam

COMPOSITION

Active ingredient: diazepam.

Excipients

Valium Tablets, 2 mg: excipients for tablets with lactose.

Valium Tablets, 5 mg: excipients for tablets with lactose.

Valium Tablets, 10 mg: colour (E132), excipients for tablets with lactose.

Valium Ampoules, 10 mg/2 ml: preservative: 95 mg sodium benzoate (E211); 5 mg benzoic acid (E210); benzyl alcohol, propylene glycol; ethyl alcohol; 2 ml water for injections.

PHARMACEUTICAL FORM AND AMOUNT OF ACTIVE INGREDIENT PER UNIT

Valium Tablets, 2 mg:	white scored **tablets** containing 2 mg diazepam.
Valium Tablets, 5 mg:	yellow scored **tablets** containing 5 mg diazepam.
Valium Tablets, 10 mg:	light-blue scored **tablets** containing 10 mg diazepam.
Valium Ampoules, 10 mg/2 ml:	clear **injection solution** containing 10 mg diazepam per 2 ml.

INDICATIONS AND POTENTIAL USES

Oral dosage forms

Symptomatic treatment of anxiety, agitation, and psychic tension resulting from psychoneurotic conditions and temporary situational disturbances. As an adjuvant in the treatment of mental and organic disorders with an anxiety component. Anxiety can manifest itself as an obviously anxious mood, as worried behaviour, and/or via functional autonomic or motor symptoms (palpitations, sweating, sleep disturbance, tremor, nervous restlessness, etc.).

Parenteral dosage form

Basic sedation prior to stressful therapeutic measures or procedures such as endoscopy, external electrical shock defibrillation, cardiac catheterisation, radiological investigations, minor surgery, reduction of dislocations and fractures, biopsies, dressing changes in burns patients, etc. in order to alleviate anxiety or acute stress reactions and to aid post-procedure amnesia.

Preoperative medication in anxious and tense patients.

Indications in psychiatry

Treatment of agitation associated with acute anxiety states and panic attacks, motor restlessness and delirium tremens.

Anticonvulsant action

Treatment of status epilepticus and other convulsive states (including tetanus).

Gynecology/obstetrics

Treatment of eclampsia, facilitation of delivery in carefully selected cases.

All dosage forms

As adjuvant therapy to relieve reflex muscle spasms associated with local trauma (wounds, inflammation) and to combat spasticity associated with damage to spinal and supraspinal interneurons; such changes can occur, for example, in spasms of cerebral origin, paraplegia, athetosis, and the stiff-man syndrome.

DOSAGE AND ADMINISTRATION

Standard dosage

In order to obtain the greatest possible benefit from the product, the dose should be carefully adjusted on an individual basis. The standard daily doses indicated below are appropriate to the needs of most patients, although higher doses may be required in certain cases.

Oral administration

Standard dosage with oral administration in adults: Initial dose: 5–10 mg. Depending on symptom severity, the standard daily dose is 5–20 mg. Individual oral doses should generally not exceed 10 mg. Time of ingestion is determined by patients' individual needs, with evening dosing being most appropriate in most cases.

Parenteral administration

If need be, in acute or critical situations or where the response to oral administration is inadequate, higher doses should be given parenterally.

The parenteral doses generally recommended in adults and adolescents range from 2 to 20 mg i.m. or i.v. depending on body weight, indication and the severity of the symptoms being treated. In certain indications (e.g. tetanus) higher doses may be required.

Intravenous injection of Valium should be slow (approx. 0.5–1 ml per minute) since over-rapid administration can cause apnea. Ready-to-use resuscitation equipment should always be at hand.

Special dosage instructions

Oral dosage forms

Dosage in children: 0.1–0.3 mg per kg body weight per day.

The tablets can be divided to facilitate dosage. In hepatic impairment particular attention must be paid to individualised dose adjustment.

Ampoules

There is evidence that diazepam can be adsorbed within plastic infusion bags and infusion sets containing PVC and leading to a reduction in diazepam concentration by 50% or more, especially where prepared bags are stored for 24 hours or more, in warm ambient conditions, or where long tubing sets or slow rates of infusion are used. PVC-containing bags and infusion sets should be avoided when infusing diazepam. When infusing diazepam caution should be exercised when switching between PVC and non-PVC-containing bags and infusion sets.

Neonates

Ampoules should be used in these patients only in the absence of alternative treatment (see *Warnings and precautions*).

Anesthesiology

Premedication: 10–20 mg (children: 0.1–0.2 mg per kg body weight) i.m. one hour before induction of anesthesia.

Induction of anesthesia: 0.2–0.5 mg per kg body weight i.v.

Basic sedation before stressful procedures and investigations: 10–30 mg (children: 0.1–0.2 mg per kg body weight) i.v.

The best method for adjusting the dosage in each patient is to give an initial injection of 5 mg = 1 ml (or 0.1 mg per kg body weight) followed by the injection of repeated doses of 2.5 mg (or 0.05 mg per kg body weight) at 30-second intervals until closure of the eyelids.

Gynecology and obstetrics

Eclampsia: for current or impending seizures, inject 10–20 mg i.v., then further doses as required i.v. or by continuous drip infusion (up to 100 mg in 24 hours).

Facilitation of delivery: 10–20 mg i.m. (in severe agitation, possibly i.v.) when the cervix is 2–5 cm dilated. Injection of 10–20 mg i.v. facilitates obstetric interventions and suturing of episiotomy wounds.

Tetanus

0.1–0.3 mg per kg body weight by i.v. injection at intervals of 1–4 hours or continuous drip infusion (3–4 mg per kg body weight within 24 hours); the same dose can also be administered simultaneously by nasoduodenal tube.

Status epilepticus

0.15–0.25 mg per kg body weight i.v. repeated if necessary after 10–15 minutes, possibly by continuous drip infusion (maximum dose: 3 mg per kg body weight in 24 hours).

Agitation

Acute anxiety states, motor restlessness, delirium tremens: initially inject 0.1–0.2 mg per kg body weight i.v.; repeat at 8-hour intervals until subsidence of acute symptoms, then continue treatment orally.

All dosage forms

Elderly patients and patients with hepatic impairment should receive a lower dose. These patients should be checked regularly at the start of treatment so that if necessary the dose can be reduced and/or the dosage interval prolonged in order to avoid overdosage as a result of product accumulation.

After about one week of treatment consideration should be given to reducing the dose.

Duration of treatment

The duration of treatment should be as short as possible. The patient should be reassessed at regular intervals and the need for continued treatment determined, especially if the patient no longer has any symptoms. The duration of treatment – the tapering-off period included – should not exceed two to three months. More prolonged treatment should be contemplated only after a reassessment of the situation. At the start of treatment it may be useful to inform the patient that the duration of treatment will be limited and to explain in detail how the dose will be tapered off.

It is also important to inform the patient of the possibility of rebound phenomena so that he/she will not be too worried should these occur. There is evidence that with short-acting benzodiazepines withdrawal phenomena can occur even within the dose interval, especially with high doses. When long-acting benzodiazepines such as diazepam are used it is mandatory to warn the patient against switching to a short-acting benzodiazepine, as this can result in withdrawal phenomena.

CONTRAINDICATIONS

Known hypersensitivity to benzodiazepines or to any excipient listed under *Composition*.

Severe respiratory failure, severe liver failure, sleep apnea syndrome and myasthenia gravis.

Benzodiazepines are not recommended for the primary treatment of psychotic disorders. Benzodiazepines should not be used for the treatment of depression or anxiety states related to depression, as such patients are at risk of suicide.

WARNINGS AND PRECAUTIONS

Simultaneous use of alcohol/central nervous system depressants

Simultaneous use of Valium and alcohol or other central nervous system depressants should be avoided. Such simultaneous use may potentiate the clinical effect of Valium. This may have certain repercussions such as severe sedation or clinically relevant depression of respiratory and/or cardiovascular function (see *Interactions*).

History of alcohol or prescription drug abuse

Valium should only be used with extreme caution in patients with a history of alcoholism, prescription drug abuse or drug addiction. Use of Valium should be avoided in patients dependent on central nervous system depressants, including alcohol.

The exception to the above is the management of acute withdrawal symptoms. The patient should be warned against simultaneous consumption of alcohol as such a combination can potentiate the undesirable effects of both substances.

Lower doses should be used in elderly or debilitated patients. Particular caution is essential when injecting Valium intravenously. Cases of apnea and cardiac arrest in particular have been reported in elderly and seriously ill patients and in patients with heart or respiratory failure.

The benzyl alcohol contained in Valium ampoules may produce irreversible lesions in neonates and in particular in premature neonates. For this reason, ampoules should only be used in these patients if there is no other alternative treatment.

Caution is required in known cardiorespiratory failure as sedatives such as Valium can exacerbate preexisting respiratory depression. On the other hand, the sedative effect can be beneficial in some patients in that it reduces the effort required for breathing.

Very small veins should not be used for injection. In particular, intra-arterial injection and extravasation should be avoided at all costs, as rapid intravenous injection in particular can lead to venous thrombosis, phlebitis, local inflammation, swelling, and in rare cases vascular changes.

In patients with impaired renal or hepatic function the standard precautionary measures should be observed.

Valium tablets contain lactose. Patients with rare congenital galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take Valium tablets.

Rebound anxiety

Rebound anxiety refers to a transient syndrome in which the symptoms that led to treatment with Valium in the first place recur with increased intensity. This can occur on discontinuation of treatment. This syndrome can also be accompanied by other reactions such as mood changes, anxiety, and restlessness.

As the risk for withdrawal phenomena and rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dose be reduced gradually.

Amnesia

It is important to bear in mind that benzodiazepines can cause anterograde amnesia. This form of amnesia can also occur at therapeutic doses, the risk increasing with increasing dose. The amnesic effects can be accompanied by odd behaviour.

Psychiatric and "paradoxical" reactions

It is known that benzodiazepine administration can cause paradoxical reactions such as agitation, irritability, aggressiveness, delusions, outbursts of rage, nightmares, hallucinations, psychoses, odd behaviour, and other behavioural disturbances. In such cases administration of the drug should be discontinued. Such reactions are more common in children and elderly.

Habituation

Response to the effect of benzodiazepines may weaken after repeated Valium use over a prolonged period.

Children and neonates

The safety and efficacy of Valium have not been studied in children under 6 months of age. Valium should be used in this age group only with the greatest caution and in the absence of alternative treatments.

Dependence

Use of benzodiazepines can lead to physical and psychological dependence. This risk is increased by prolonged use and high doses and in patients with known alcoholism and/or prescription drug abuse or drug addiction. Withdrawal phenomena occur especially after abrupt treatment discontinuation and are limited in milder cases to tremor, agitation, sleep disturbance, anxiety, headache, and impairment of concentration. However, other symptoms such as sweating, muscle and abdominal cramps, perceptual disturbances, and in rare cases delirium and convulsions may occur.

Depending on the duration of action of the substance, withdrawal phenomena appear a few hours to a week or even more after discontinuation of treatment.

In order to minimise the risk of dependence, benzodiazepines should be prescribed only after a careful consideration of the indication and should be taken for as short a period as possible (generally no longer than four weeks when used as a hypnotic, for example). The need for continuation of treatment should be reviewed regularly. The risk-benefit relationship of more prolonged treatment is less clear, hence it is indicated only in certain patients (e.g. those with panic attacks).

In order to avoid withdrawal symptoms, treatment should be discontinued by tapering the dose in all patients. Should withdrawal symptoms occur nonetheless, close medical monitoring and support of the patient are required.

INTERACTIONS

Pharmacokinetic interactions (drug-drug interactions [DDI])

Oxidative metabolism of diazepam leading to the formation of N-desmethyldiazepam, 3-hydroxydiazepam (temazepam) and oxazepam depends on the CYP2C19 and CYP3A isoenzymes of cytochrome P450. In-vitro studies have shown that the CYP3A isoform is mainly responsible for hydroxylation while both CYP3A and CYP2C19 are responsible for N-demethylation. The results of in-vivo studies conducted in volunteers have confirmed the in-vitro results. Substrates modulating CYP3A and/or CYP2C19 may in some circumstances influence the pharmacokinetics of diazepam. Inhibitors of CYP3A and CYP2C19 such as cimetidine, ketoconazole, fluvoxamine, topiramate, fluoxetine and omeprazole may produce more potent and longer sedation. In addition, according to some reports, diazepam modifies the metabolic elimination of phenytoin.

Tablets

Cisapride can cause a temporary increase in the sedative effects of orally administered benzodiazepines, as it accelerates their absorption.

Pharmacodynamic interactions (DDI)

The effects on sedation, respiration and hemodynamics may be potentiated when taking Valium with central depressants such as neuroleptics, anxiolytics/sedatives, antidepressants, hypnotics, anticonvulsants, opioids, anesthetics and sedative antihistamines, and similarly when Valium is taken together with alcohol.

Patients receiving Valium should avoid taking alcohol (see *Warnings and precautions*).

For other remarks on other central depressants, including alcohol, see *Overdosage*.

Theophylline may inhibit the action of diazepam.

On the other hand, no interactions with commonly used antidiabetic agents, anticoagulants or diuretics are known.

Rifampicin is a potent hepatic enzyme inducer. This may accelerate diazepam metabolism in the liver.

When Valium is given in combination with opiates that cause respiratory depression, the possibility of potentiation of the respiratory depressant effect should be borne in mind.

PREGNANCY AND LACTATION

Pregnancy

Valium should not be used during pregnancy unless it is clearly required.

Diazepam and its metabolites cross the placenta.

Prolonged administration of benzodiazepines during pregnancy can result in hypotension, respiratory failure, and hypothermia in the neonate. With this category of drugs, withdrawal phenomena have also been reported occasionally in neonates. Particular

caution is required when Valium is used during labour and delivery, as high individual doses can cause irregularities of heart rate in the unborn child and hypotonia, poor sucking, hypothermia, and moderately severe respiratory depression in the neonate (floppy infant syndrome). It must be borne in mind that the enzyme system responsible for the degradation of diazepam is not yet fully developed in neonates (especially premature neonates).

Lactation

Diazepam and its metabolites are excreted in breast milk. Where use of Valium is absolutely essential during lactation, breast-feeding should be discontinued.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Valium has a pronounced influence on the ability to drive and use machines. Patients taking Valium should be warned against performing activities that require full mental alertness; these include the operation of dangerous machines and the driving of motor vehicles. Patients taking Valium should also be warned against simultaneous consumption of alcoholic beverages, as such a combination can potentiate the undesirable effects of both types of substances.

UNDESIRABLE EFFECTS

The most frequently reported undesirable effects are fatigue, clouding of consciousness and muscle weakness; these effects are normally dose-related. These reactions occur mainly on starting treatment and generally resolve on prolonged use.

Tablets and ampoules

Blood and lymphatic system

Elevation of alkaline phosphatase blood levels during i.v. administration.

Psychiatric disorders

Based on the experience acquired, paradoxical reactions such as anxiety, agitation, irritability, aggressiveness, delusions, anger, nightmares, hallucinations, psychoses, odd behaviour and other undesirable behavioural effects can occur with use of benzodiazepines. In such cases the drug should be discontinued. The probability of such an effect developing is greater in children and the elderly.

Confusion, emotional impoverishment, decreased vigilance, depression, increase or decrease in libido.

Chronic use (even at therapeutic doses) may lead to the development of physical dependence. Discontinuation of the therapy may result in withdrawal or rebound symptoms (see under *Warning and precautions / History of alcohol or prescription drug abuse* and *Dependence*).

Abuse of benzodiazepines has been reported (see under *Warnings and precautions* / *Dependence*).

Musculoskeletal system

Muscle weakness. There have been reports of falls and fractures in benzodiazepine users. The risk is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.

Gastrointestinal disorders

Nausea, pelvic pain, diarrhea, dry mouth, constipation, hypersalivation and gastrointestinal disorders.

Eyes

Diplopia, blurred vision.

Vascular disorders

Hypotension, circulatory depression.

Investigations

Irregular pulse, elevated transaminases in rare cases, elevated alkaline phosphatase.

Kidneys and urinary tract

Incontinence, urinary retention.

Skin

Rashes.

Ear

Dizziness.

Heart

Heart failure, including cardiac arrest.

Respiratory organs

Respiratory depression, including respiratory arrest.

Liver and biliary tract

Jaundice in rare cases.

Ampoules only

Systemic disorders and injection site reactions

Venous thrombosis, phlebitis, irritation at the injection site, local swelling and, less frequently, vascular changes may occur, in particular after rapid i.v. injection.

Very small veins should not be used for injection; in particular intra-arterial injection and extravasation should be strictly avoided.

Intramuscular injection may cause local irritation and erythema may occur at the injection site in some cases. Tenderness is relatively common.

Heart and circulation / Respiration

Cardiorespiratory depression may occur after rectal diazepam administration.

OVERDOSAGE

Symptoms

In overdosage, benzodiazepines often lead to clouding of consciousness, ataxia, dysarthria and nystagmus. Overdosage of Valium alone is rarely life-threatening but it can cause areflexia, apnea, hypotension, cardiorespiratory depression and coma. If coma occurs it generally lasts only a few hours but it may also be more protracted and cyclical, in particular in elderly patients. Benzodiazepine-induced respiratory depression is more serious in patients with respiratory tract disease.

Benzodiazepines potentiate the effect of other central depressants, including alcohol.

Treatment

Monitor the patient's vital functions and institute the supportive measures indicated by the patient's clinical status. In particular symptomatic treatment of the cardiorespiratory and central nervous system effects may prove necessary in such patients.

Additional absorption should be prevented using appropriate methods, e.g. treatment with activated charcoal within 1–2 hours. If activated charcoal is used, airway protection is mandatory in semi-comatose patients. Gastric lavage can be considered in cases of mixed ingestion, but not as a routine measure.

If central nervous system depression is severe consider the use of flumazenil (Anexate®), a benzodiazepine antagonist. However, this should only be administered under closely monitored conditions since it has a short half-life (about one hour), therefore patients administered flumazenil will require monitoring after its effects have worn off. Caution is mandatory when using flumazenil in epileptics treated with benzodiazepines. Flumazenil must be used with the greatest caution after the ingestion of drugs that reduce the seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil (Anexate®) for further information on the correct use of this drug.

PROPERTIES AND EFFECTS

ATC code: N05BA01.

Mechanism of action/Pharmacodynamics

The active ingredient of Valium is a member of the benzodiazepine group of tranquillisers, which possess anxiolytic, sedative, muscle-relaxant, and anticonvulsant

properties. These actions are now known to be due to potentiation of the effect of γ-aminobutyric acid (GABA), the most important inhibitory neurotransmitter in the brain.

PHARMACOKINETICS

Absorption

The active ingredient of Valium is rapidly and completely absorbed from the digestive tract, peak plasma concentrations being reached 30–90 minutes after oral administration. Intramuscular injection is likewise followed by complete absorption, though not always more rapidly than with oral administration.

Distribution

Diazepam and its metabolites are highly bound to plasma proteins (diazepam: 98%).

Diazepam and its metabolites cross the blood-brain barrier and the placenta. They are also detectable in breast milk in concentrations approximately 10–20% (diazepam) and 10–30% (nordiazepam) of those in maternal plasma. The steady-state volume of distribution is 0.8–1.0 l/kg. The distribution half-life is up to 3 hours.

Metabolism

Diazepam is metabolised to the pharmacologically active substance nordiazepam ($t_{½β}$ = 96 hours), hydroxydiazepam and oxazepam.

Oxidative metabolism of diazepam depends on the CYP3A and CYP2C19 isoenzymes. Oxazepam and temazepam are then conjugated to glucuronic acid.

Elimination

The elimination curve of diazepam is biphasic, consisting of an initial distribution phase with a half-life of up to 3 hours and a terminal elimination phase with a half-life of up to 48 hours.

Elimination is mostly (about 70%) via the urine in the form of free or (mostly) conjugated metabolites. The clearance of diazepam is 20–30 ml/min.

Pharmacokinetics in special patient populations

The elimination half-life can be prolonged in neonates, the elderly and patients with hepatic dysfunction; it should therefore be borne in mind that plasma concentrations may, in such patients, only reach steady state with a certain delay.

The half-life of diazepam is unaltered in renal failure.

Diazepam and its active metabolite nordiazepam accumulate after repeated administration.

After about one week of treatment consideration should be given to reducing the dose.

PRECLINICAL DATA

Carcinogenicity

The carcinogenic potential of orally administered diazepam has been examined in various rodent species. The incidence of hepatocellular carcinoma increased in male mice. No significant increase was observed in the incidence of the tumours in female mice, rats, hamsters or Mongolian gerbils.

Mutagenicity

A number of studies have provided weak evidence of mutagenic potential at high concentrations which, however, were far above therapeutic doses in humans.

Impairment of fertility

Reproductive studies in rats showed decreases in the number of pregnancies and in the number of surviving offspring following administration of oral doses of 100 mg/kg/day to both males and females prior to and during mating and throughout gestation and lactation.

Teratogenicity

Diazepam was found to be teratogenic in mice at doses of 45–50 mg/kg/day, 100 mg/kg/day and 140 mg/kg/day, and in hamsters at a dose of 280 mg/kg. However, no teratogenicity was observed when diazepam was administered to rats at doses of 80 and 300 mg/kg/day or to rabbits at doses of 20 and 50 mg/kg/day.

SPECIAL REMARKS

Incompatibilities

Valium ampoules can be diluted with the following solutions for infusion: 0.9% sodium chloride, 5% glucose and 10% glucose.

Opened ampoules have been shown to be chemically and physically stable for 24 hours at ambient temperature.

From a microbiological point of view, however, the product should be used immediately unless the dilute solution is prepared under controlled and validated aseptic conditions.

Use of PVC-containing containers and infusion sets may result in decreased concentrations of diazepam (see *Special dosage instructions, Ampoules*).

Stability

The medicine should not be used after the expiry date (EXP) shown on the pack. The contents must not be used if cloudy.

Special instructions for storage

Valium tablets, 2 mg, 5 mg and 10 mg: Do not store above 30 °C.

Valium ampoules, 10 mg/2 ml: Store below 30 °C and protect from light.

Special precautions for disposal

At the end of treatment return unused or expired medication in its original pack to the point of sale (physician or pharmacist) for appropriate disposal.

PACKS

Valium 2 Roche	
Tablets (scored, white), 2 mg	30, 100
Valium 5 Roche	
Tablets (scored, yellow), 5 mg	25, 100
Valium 10 Roche	
Tablets (scored, light blue), 10 mg	25, 100
Ampoules (2 ml), 10 mg	5, 10

Medicine: keep out of reach of children

Current at: March 2013

Ampoules:

Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland

by CENEXI SAS, Fontenay-sous-Bois, France

2 mg tablets:

Made in Switzerland by F. Hoffmann-La Roche Ltd, Basel

5 mg and 10 mg tablets:

Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland

by Roche Farma SA, Leganés, Spain