PROFESSIONAL INFORMATION LEAFLET

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

VALIUM® 5 mg tablet

VALIUM® 10 mg tablet

VALIUM® 10 mg/2 mL injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VALIUM contains as active substance diazepam chemically known as 7-chloro-1, 3-dihydro-1-methyl-5-phenyl- 2H-1,4-benzodiazepin-2-one.

Tablets

Each 5 mg tablet contains 5 mg diazepam.

Each 10 mg tablet contains 10 mg diazepam.

Contains sugar (lactose monohydrate 100 mg per tablet).

For the full list of excipients, see section 6.1.

Injection in Ampoules

Each ampoule contains 10 mg diazepam per 2 mL.

VALIUM injection contains 8,5 % ethyl alcohol. Contains benzyl alcohol as a vehicle.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets: All tablet strengths have an 8 mm diameter. All tablet dosage forms are embossed with the strength of the tablet and V e.g. '5 V'. The reverse sides are scored.

Colour identification is as follows:

VALIUM 5 mg tablet: Yellow.

VALIUM 10 mg tablet: Light blue.

VALIUM 10 mg/2 mL injection: Greenish-yellow solution in 2 mL colourless glass ampoules.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

VALIUM is only indicated when the disorder is severe, disabling or when the individual is subject to extreme stress.

VALIUM is indicated for the following conditions:

Tablets

Anxiety: symptomatic relief of anxiety, tension and other somatic or psychological complaints associated with the anxiety syndrome. It can also be used as an adjunct to the treatment of anxiety or excitation associated with psychiatric disorders.

Muscle relaxation: as an adjunct for the relief of reflex muscle spasm due to local trauma (injury, inflammation). It can also be used to combat spasticity arising from damage to spinal and supraspinal interneurons such as cerebral palsy and paraplegia, as well as athetosis and stiff-man syndrome.

Treatment should be as short as possible. The patient should be reassessed regularly and the need for continued treatment should be evaluated especially when the patient is symptom-free. The overall duration of treatment of anxiety should not be more than 8 to 12 weeks, including a tapering off process. In certain cases, extension beyond the maximum treatment period may be necessary. If so, it should not take place without re-evaluation of the patient's status.

Injection in Ampoules

Conscious sedation: diagnostic and therapeutic interventions such as cardioversion, cardiac catheterisation, endoscopy, radiological procedures, minor surgical interventions, reduction of dislocations and fractures, biopsies and dressing of burns, etc. in order to relieve apprehension, anxiety, acute stress and to diminish recollections of such procedures.

Premedication of anaesthesia: allaying anxiety and tension prior to surgical procedures.

Excitation: the treatment of excitation states associated with psychiatric disorders, including acute anxiety and panic, as well as in motor unrest and delirium tremens.

Anti-convulsant effect: the treatment of status epilepticus and other convulsive states.

Gynaecology and obstetrics: second line treatment of seizures in eclampsia (if magnesium sulphate is unavailable or if seizures continue despite administration of magnesium sulphate).

Muscle relaxation: as an adjunct for the relief of reflex muscle spasm (including tetanus) due to local trauma (injury, inflammation). It can also be used to combat spasticity arising from damage to spinal and supraspinal interneurons such as cerebral palsy and paraplegia, as well as athetosis and stiff-man syndrome.

4.2. Posology and method of administration

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 8 – 12 weeks, including the tapering-off period. Extension beyond this period should not take place without re-evaluation 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 minimising anxiety over such symptoms, should they occur during withdrawal. There is evidence that, in 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 short-acting benzodiazepines as withdrawal symptoms may develop.

Tablets

The tablet can be divided into equal halves to facilitate dosing.

Standard adult dosage

For optimal effect, the dosage should be carefully individualised. Treatment should begin at the lowest effective dose appropriate to the particular condition.

Average adult dosage for oral administration: Initial dose: 5 - 10 mg. Depending on symptom severity, the usual dose is 5 - 20 mg daily. The maximum single oral dose for adults should not normally exceed 10 mg.

Special dosage instructions

Chronic respiratory depression, elderly and debilitated patients

Elderly and debilitated patients who are at particular risk of oversedation, respiratory depression and ataxia should be given half of the usual adult dose. These patients should be checked regularly at the start of treatment in order to minimise the dosage and/or frequency of administration to prevent overdose due to accumulation (see section 5.2).

Hepatic impairment

Patients with severe hepatic impairment should not be treated with VALIUM tablets (see section 4.3). In patients with mild or moderate hepatic impairment, the lowest dose possible should be given.

Renal Impairment

The usual precautions in treating patients with impaired renal function should be observed.

Paediatric use

Children's dosage: 0,1 - 0,3 mg/kg bodyweight daily.

VALIUM should not be given to children without careful assessment of the indication; the duration of treatment must be kept to a minimum.

Safety and efficacy have not been demonstrated in children below 6 months of age.

Injection in Ampoules

Warning

I.V. injection of VALIUM should always be slow (approximately 0,5 - 1,0 mL/min) as excessively rapid administration can lead to apnoea; resuscitation apparatus must be kept ready at all times.

Standard adult dosage

For optimal effect, the dosage should be carefully individualised. The usual daily doses given below will meet the needs of most patients, though there will be cases requiring higher doses. In adults and juveniles, a parenteral dose 2 - 20 mg i.m. or i.v. is generally recommended, depending on bodyweight, indication and severity of symptoms. In some indications (e.g. tetanus) higher doses may occasionally be required.

Special dosage instructions

Elderly and debilitated patients

Elderly patients should be given a reduced dose. These patients should also be checked regularly at the start of treatment in order to minimise the dosage and/or the frequency of administration to prevent overdose due to accumulation (see section 5.2).

Hepatic Impairment

Patients with severe hepatic impairment should not be treated with VALIUM tablets (see section 4.3). In patients with mild or moderate hepatic impairment, the lowest dose possible should be given. These patients should also be checked regularly at the start of treatment in order to minimise the dosage and/or the frequency of administration to prevent overdose due to accumulation (see section 5.2).

Renal Impairment

The usual precautions in treating patients with impaired renal function should be observed.

Anaesthesiology

Premedication: 10 mg i.m.; children 0,1 - 0,2 mg/kg bodyweight, 1 hour before induction of anaesthesia. Conscious sedation before stressful therapeutic interventions: 10 mg i.m.; children 0,1 - 0,2 mg/kg bodyweight. Adapting the dose to the patient’s individual needs consists of an initial injection of 5 mg (1 mL), or 0,1 mg/kg bodyweight in children, followed every 30 seconds by increments of 50 % of the initial dose.

Gynaecology and obstetrics

Eclampsia: For actual or threatened convulsions where magnesium sulphate cannot be used: 10 - 20 mg i.v.; additional doses, as required, either i.v. or by continuous infusion (up to 100 mg in 24 hours). If seizures continue despite the administration of magnesium sulphate, VALIUM can be administered at a dose of 5 – 10 mg i.v.

Tetanus

A dosage of 0,1 - 0,3 mg/kg bodyweight should be given i.v. in intervals of 1 - 4 hours. Alternatively by continuous infusion or by gastric tube (3 - 4 mg/kg bodyweight in 24 hours).

Status epilepticus

Anticonvulsant effect in status epilepticus: 0,15 - 0,25 mg/kg bodyweight should be given i.v., repeated as necessary after 10 - 15 minutes, or by continuous infusion. Maximum dose: 3 mg/kg bodyweight in 24 hours.

Excitation states

Excitation in acute anxiety states, motor unrest or delirium tremens: Initially 0,1 - 0,2 mg/kg bodyweight i.v., repeated at 8 hourly intervals until acute symptoms subside, after which, treatment should be continued orally.

4.3. Contraindications

VALIUM is contraindicated in patients with:

- a known history of hypersensitivity to benzodiazepines or any of the excipients;
- severe respiratory insufficiency;
- severe hepatic impairment as benzodiazepines may precipitate hepatic encephalopathy;
- sleep apnoea syndrome;
- myasthenia gravis.

VALIUM is not recommended for the primary treatment of psychotic illness.

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

Dependence on other CNS depressants including alcohol, except in the acute withdrawal reactions. (See section 4.4).

4.4. Special warnings and precautions for use

Concomitant use of alcohol/CNS depressants

The concomitant use of VALIUM with alcohol or/and CNS depressants should be avoided.

Such concomitant use has the potential to increase the clinical effects of VALIUM possibly including severe sedation that could result in coma or death, clinically relevant respiratory and/or cardiovascular depression (See section 4.5 and 4.9).

Risk from concomitant use of opioids

Concomitant use of diazepam and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as diazepam with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe diazepam concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

Medicine abuse and dependence

Medical history of alcohol or drug abuse

VALIUM should be used with extreme caution in patients with a history of alcohol or drug abuse, see Dependence below.

VALIUM should be avoided in patients with dependence on CNS depressants including alcohol. (See section 4.3).

An exception to the latter is the management of acute withdrawal reactions.

Dependence

There is a potential for abuse and the development of physical and psychological dependence, especially with prolonged use and high doses.

The risk of dependence is greater in patients with a medical history of alcohol and/or drug abuse. VALIUM should be used with extreme caution in patients with a history of alcohol or drug abuse.

Abuse of benzodiazepines has been reported in poly-drug abusers.

Withdrawal

Once physical dependence had developed, abrupt termination of treatment will be accompanied by withdrawal symptoms.

These may consist of headache, diarrhoea muscle pain, convulsions, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases, the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of extremities, hypersensitivity to light, noise and physical contact, hallucinations or convulsions.

Withdrawal symptoms may occur after long periods of ordinary therapeutic doses.

VALIUM may increase the frequency and severity of attacks of grand mal epilepsy, during treatment or abrupt withdrawal.

When benzodiazepines are used, withdrawal symptoms may develop when switching from a long-acting benzodiazepine, like diazepam (see section 5.2) to a benzodiazepine with a considerably shorter elimination half-life.

Rebound anxiety

A transient syndrome, whereby the symptoms that led to treatment with VALIUM, recur in an enhanced form 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 gradually decreased.

Hepatic impairment

Benzodiazepines may have a contributory role in precipitating episodes of hepatic encephalopathy in severe hepatic impairment. VALIUM is therefore contraindicated in patients with severe hepatic insufficiency (see section 4.3). Special caution should be exercised when administering VALIUM to patients with mild to moderate hepatic impairment (see section 4.3).

Psychiatric and ‘paradoxical’ reactions

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, anxiety, delusion, anger, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using VALIUM.

Should this occur, the use of VALIUM should be discontinued.

They are more likely to occur in children and in the elderly.

Amnesia

It should be borne in mind that VALIUM may induce anterograde amnesia.

Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour.

Tolerance

Some loss of response to the effects of VALIUM may develop after repeated use for a prolonged period of time.

Paediatric use

VALIUM should be used in paediatrics with extreme caution and only when other therapeutic alternatives are not available. Safety and effectiveness in paediatric patients below the age of 6 months have not been established (see section 4.2).

Use in the elderly and debilitated patients

Extreme care must be used when using VALIUM, particularly by the i.v. route, in the elderly, in very ill patients and to those with limited pulmonary reserve because of the possibility that apnoea and/or cardiac arrest, and prolonged sedation and confusion may occur. See also section 4.2.

Respiratory Insufficiency

A lower dose is recommended for patients with chronic respiratory insufficiency, due to the risk of respiratory depression (see section 4.3).

Sleep apnoea

VALIUM is contraindicated in patients with sleep apnoea due to possible additive effects on respiratory depression (see section 4.3).

Myasthenia gravis patients

Extreme caution should be taken when using VALIUM to a patient with myasthenia gravis, owing to pre-existing muscle weakness. (See section 4.3).

Ampoules

Injection into very small veins and intra-arterial injection

Very small veins should not be selected for injection.

In particular, intra-arterial injection or extravasation must be strictly avoided, because venous thrombosis, phlebitis, local irritation, swelling or less frequently, vascular changes may occur particularly after rapid i.v. injection.

Plastic materials

VALIUM is adsorbed to plastic infusion bags and infusion sets especially those containing polyvinyl chloride (PVC), leading to a reduction in VALIUM concentration by 50 % or more, especially where prepared bags are stored in warm ambient conditions, or where long tubing sets or slow rates of infusion are used.

If possible PVC-containing bags and infusion sets should be avoided when infusing VALIUM (see section 6.6).

When infusing VALIUM caution should be exercised when switching between PVC and non-PVC-containing bags and infusion sets.

Ingredients

The benzyl alcohol (an excipient) contained in VALIUM injection may lead to irreversible damage (including metabolic acidosis, respiratory depression and convulsion) in the newborn, especially in the premature.

Therefore, for these patients the ampoules should only be used if no therapeutic alternative is available.

Given intravenously, effects on the cardiovascular system can occur; this may consist of a decrease in blood pressure, left ventricular stroke work and an increase in heart rate.

Tablets

Lactose

Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take VALIUM.

Caution should be observed in patients suffering from anxiety accompanied by an underlying depressive disorder.

The action of other central nervous system depression substances such as narcotics, barbiturates and monoamine oxidase inhibitors may be enhanced. (See section 4.3).

Withdrawal should be gradual in patients receiving high doses for prolonged periods of time.

Patients should be cautioned regarding the additive effect of alcohol.

VALIUM should be given with caution to the elderly, and to patients with hepatic or renal dysfunction, obstructive airways disease and arteriosclerosis.

VALIUM should be given with caution to infants, who may not be able to metabolise diazepam. (See section 4.6).

4.5. Interaction with other medicinal products and other forms of interaction

Opioids

The concomitant use of sedative medicines such as benzodiazepines or related drugs such as diazepam with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

Pharmacokinetic interactions

The metabolism of diazepam and its main metabolite, DMDZ depends on the cytochrome P450 isozymes CYP3A4 and CYP2C19. Modulators of these enzymes may lead to changes in diazepam disposition and effects. Strong interactions are seen with compounds which affect both of diazepam's oxidative metabolic pathways simultaneously; moderate effects only occur even with strong inhibitors if they affect only one of diazepam's metabolic pathways. Inhibitors of CYP3A4 and CYP2C19 decrease metabolic rate and may led to higher than normal concentrations of diazepam and the desmethyl metabolite and consequently to increased/ prolonged sedation and anxiolytic effects. Such changes may exacerbate diazepam's effects in patients with increased sensitivity, e.g. due to their age, reduced liver function or treatment with other medicines that impair oxidation. Inducers of CYP3A4 and CYP2C19 may lead to lower than expected concentrations and hence to a lack of desired efficacy.

Effect of other medicines on the pharmacokinetics of diazepam

Enzyme Inhibitors

The following therapeutic classes/medicines can provoke increased and prolonged sedation (see also Interactions with food):

Azole derivatives

Antimycotic azole derivatives inhibit CYP3A4 and CYP2C19 pathways and lead to increased exposure to diazepam (diazepam AUC ratio fluconazole 2,5; voriconazole 2,2) and prolonged elimination half-life of diazepam (with fluconazole from 31 h to 73 h; with voriconazole from 31 h to 61 h). The influence of the antimycotics on diazepam levels was only seen at 4 hours after administration and beyond. Itraconazole has a more moderate effect with no clinically significant interaction with diazepam as determined by psychomotor performance tests.

Serotonin reuptake inhibitors

The serotonin reuptake inhibitor fluvoxamine is also an inhibitor of both of diazepam's degradation pathways and increased not only exposure to diazepam by 180 % and prolonged its elimination half-life from 51 h to 118 h, but also increased exposure and time to reach steady state of the desmethyl metabolite. Fluoxetine showed a more moderate effect on diazepam AUC (approximately 50 % increase) and did not affect psychomotor response because combined concentrations of diazepam and desmethyl-diazepam were similar with and without fluoxetine.

Contraceptives

Combined hormonal contraceptives appear to reduce the clearance (by 67 %) and prolong elimination half-life (by 47 %) of diazepam. 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. A medicine interaction causing pregnancy was not observed.

Proton pump inhibitors

The proton pump inhibitor omeprazole, a CYP2C19 and CYP3A4 inhibitor, administered at a dose of 20 mg once daily increased the diazepam AUC by 40 % and the half-life by 36 %, at a dose of 40 mg once

daily omeprazole increased the diazepam AUC by 122 % and the half-life by 130 %. The elimination of desmethyl-diazepam was reduced as well. The effect of omeprazole was only seen in extensive but not slow metabolisers of CYP2C19. Esomeprazole (but not lansoprazole or pantoprazole) has the potential to inhibit the metabolism of diazepam to a similar degree as omeprazole.

Histamine H2-receptor antagonists

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 by 40 to 50 %. The effect is no different after one day or after chronic treatment with cimetidine and results in higher exposure to and a prolonged elimination half-life of diazepam and its main metabolite after single dosing and to higher steady-state concentrations after multiple dosing of diazepam. Enhanced sedation was seen with co-administration of cimetidine. No such pharmacokinetic interaction was seen with the H2-antagonists ranitidine and famotidine.

Disulfiram

Disulfiram inhibits the metabolism of diazepam (median decrease in clearance 41 %, increase in half-life 37 %) and probably the further metabolism of diazepam's active metabolites. Enhanced sedative effects may result.

Isoniazid

Antituberculosis therapy may change the disposition of diazepam. In presence of isoniazid diazepam mean exposure (AUC) and half-life were increased (on average 33 - 35 %) with the largest changes seen in subjects with slow-acetylator phenotype.

Diltiazem

The calcium channel blocker diltiazem, a substrate for the same CYP isozymes as diazepam and an inhibitor of CYP3A4, increased AUC (by approximately 25 %) and prolonged half-life (by 43% in extensive CYP2C19 metabolisers) of diazepam with little differences between subjects with different CYP2C19 phenotypes. In the presence of diltiazem exposure to desmethyl-diazepam also tended to increase.

Idelalisib

The primary metabolite of idelalisib is a strong CYP3A4 inhibitor and increases the serum concentrations of diazepam so that dose reduction may have to be considered.

Psychostimulants

The psychostimulants modafinil and armodafinil induce CYP3A4 and inhibit CYP2C19; they may prolong the elimination of diazepam and cause excessive sedation.

Enzyme inducers

The following therapeutic classes/medicines can lead to decreased plasma concentrations and as such decreased effectiveness of diazepam; monitor for loss of efficacy:

Rifampicin

Rifampicin very potently induces CYP3A4 and has also a significant accelerating effect on the CYP2C19 pathway. When dosed at 600 mg daily for 7 days, VALIUM clearance was increased 4,3-fold and AUC decreased by -77 %. A significant reduction in exposure to all diazepam metabolites was also observed. Doubling the daily rifampicin dose did not further increase its effect.

Carbamazepine

Carbamazepine is a known inducer of CYP3A4 and accelerated elimination (increased clearance, reduced half-life) of diazepam 3-fold while increasing concentrations of desmethyl-diazepam.

Other Pharmacokinetic interactions

Antacids

Antacids may lower the rate but will not lower the extent of diazepam absorption from the tablet; this may lead to attenuated effects after a single dose but not influence steady-state concentrations during multiple-dose therapy.

Prokinetic medicines

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

Intravenous but not oral metoclopramide increases the rate of absorption of diazepam and increases the maximum concentration achieved after oral dosing.

Narcotics

Narcotics (morphine, pethidine) decrease the absorption rate and lower peak concentrations of orally administered diazepam.

Effect of diazepam on the pharmacokinetics of other medicines

Ketamine

Diazepam pre-treatment changes the pharmacodynamics and pharmacokinetics of the anaesthetic ketamine. Ketamine N-demethylation was inhibited leading to a prolonged half-life and prolonged ketamine-induced sleeping time. In the presence of diazepam, a reduced ketamine concentration is required to achieve adequate anaesthesia.

Phenytoin

Phenytoin therapy was associated with higher concentrations and increased phenytoin intoxication when combined with diazepam. However some authors have found no interaction or even lowered plasma concentrations of phenytoin when co-administered with diazepam.

Pharmacodynamic Interactions

Opioids

Diazepam boosts the subjective opioid effects of methadone. It increases methadone effects on pupil diameter and sedation and also causes significantly greater deterioration in reaction time when compared to methadone alone. No pharmacokinetic interaction occurs between the two medicines.

Alcohol and other CNS depressants

Alcohol and other CNS depressants should be avoided in patients receiving VALIUM. (See sections 4.4 and 4.9).

Enhanced side effects such as sedation and cardio-respiratory depression may also occur when VALIUM is co-administered with other centrally acting depressants such as antipsychotics, anxiolytics or

sedatives, antidepressants, hypnotics, anticonvulsants, narcotic analgesics, anaesthetics and sedative antihistamines, barbiturates or alcohol.

There are several reports of severe hypotension, respiratory depression or loss of consciousness in patients under combined treatment with clozapine and benzodiazepines, including diazepam.

Additive CNS depressant effects can be expected when combining phenothiazines and benzodiazepines; sedation, respiratory depression and airway obstruction has been reported with the combined use of levopromazine and diazepam.

Additive effects of olanzapine and diazepam on sedation and hypotension occur in the absence of a pharmacokinetic interaction. Concomitant parenteral use is not recommended.

Antiparkinsonian agent

Reversible loss of control of Parkinson's disease has been seen in some patients treated with combined levodopa and diazepam. This might be caused by decreased striatal dopamine levels.

Xanthines

The xanthines theophylline and caffeine oppose the sedative and possibly anxiolytic effects of diazepam partially through blocking of adenosine receptors.

Interactions with food

Grapefruit juice contains strong inhibitors of CYP3A4. Diazepam exposure was strongly increased (AUC 3,2-fold; C_{max} 1,5-fold) and time to reach maximum concentration was delayed when diazepam was given with grapefruit juice instead of water.

Food and antacids may lower the rate but will not lower the extent of diazepam absorption from the tablet; this may lead to attenuated effects after a single dose but not influence steady-state concentrations during multiple-dose therapy.

DILATREND may potentiate the effect of other concomitantly administered medicines that are antihypertensive in action or have hypotension as part of their adverse effect profile.

4.6. Fertility, pregnancy and lactation

Pregnancy

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.

Continuous administration of benzodiazepines during pregnancy may give rise to the so-called floppy-infant syndrome, manifested by hypotension, reduced respiratory function and hypothermia in the newborn child (see section 5.2).

Withdrawal symptoms in newborn infants have been reported with VALIUM.

Special care must be taken when VALIUM is used during labour and delivery, as high single doses may produce irregularities in the foetal 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 medicine is not yet fully developed (especially in premature infants).

Breastfeeding

Since diazepam passes into breast milk, VALIUM should not be administered to breast feeding mothers.

Women of childbearing potential

If VALIUM is prescribed to a woman of childbearing potential, she should be advised to contact her medical practitioner regarding discontinuation of VALIUM, if she intends to become or suspects that she is pregnant.

4.7. Effects on ability to drive and use machines

Sedation, amnesia, impaired concentration and impaired muscle function may adversely affect the ability to drive or operate machinery. Prior to receiving VALIUM, the patient should be warned not to drive a vehicle or operate a machine until completely recovered.

If sleep duration is insufficient or alcohol is consumed, the likelihood of impaired alertness may be increased (see section 4.5).

4.8. Undesirable effects

Summary of the safety profile

Fatigue, drowsiness and muscle weakness are usually dose-related. Drowsiness is more common in elderly and debilitated patients and in those receiving high doses.

Description of selected adverse reactions

Psychiatric disorders

Less frequent:

Paradoxical reactions such as restlessness, agitation, irritability, disorientation, aggressiveness, nervousness, hostility, anxiety, delusion, anger, nightmares, abnormal dreams, hallucinations, psychoses, hyperactivity, inappropriate behaviour and other adverse behavioural effects are known to occur.

Drowsiness, confusional state, numbed emotions and mood disturbances, depression, reduced alertness, changes in libido.

Physical and psychic dependence (see section 4.4).

Nervous system disorders

Less frequent:

Headache, ataxia, dizziness, hypersalivation, slurred speech, dysarthria, tremor, anterograde amnesia, decreased alertness. VALIUM may increase the frequency and severity of attacks of grand mal epilepsy, during treatment or abrupt withdrawal.

Eye disorders

Less frequent:

Diplopia, blurred vision.

Ear and labyrinth disorders

Less frequent:

Vertigo.

Cardiac disorders

Less frequent:

Cardiac failure including cardiac arrest.

Vascular disorders

Less frequent:

Hypotension, circulatory depression.

Respiratory, thoracic and mediastinal disorders

Less frequent:

Respiratory depression including respiratory failure due to a depressant effect on the respiratory centre and cardiovascular collapse, may occur following intravenous and intramuscular administration. Cardio-respiratory depression may occur if VALIUM is administered rectally.

Gastrointestinal disorders

Less frequent:

Constipation, nausea. dry mouth.

After several days of high doses of VALIUM injection, diarrhoea, sometimes accompanied by colic-like stomach pains, may occur.

Hepato-biliary disorders

Less frequent:

Jaundice.

Skin and subcutaneous tissue disorders

Less frequent:

Skin reactions.

Renal and urinary disorders

Less frequent:

Incontinence, urinary retention.

General disorders and administration site conditions:

Frequent:

Venous thrombosis, phlebitis, local irritation, swelling, tenderness.

Less frequent:

Vascular changes, particularly after rapid i.v. injection. I.m. injection can result in local pain, in some cases accompanied by erythema at the site of injection, fatigue.

Investigations

Less frequent:

Variations in pulse rate, elevated transaminases and alkaline phosphatase.

Injury, poisoning and procedural complications

Less frequent:

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9. Overdose

Symptoms

Manifestations of overdosage include somnolence, confusion, coma, respiratory and cardiovascular depression and hypotension.

VALIUM commonly cause drowsiness, ataxia, dysarthria and nystagmus.

Overdose of VALIUM may be life-threatening if the medicine is taken alone, and may lead to areflexia, apnoea, hypotension, cardiorespiratory depression and coma. Coma, if it occurs, usually lasts a few hours but it may be more protracted and cyclical, particularly in elderly patients. VALIUM respiratory depressant effects are more serious in patients with respiratory disease. VALIUM increase the effects of other central nervous system depressants, including alcohol.

Treatment

Monitor the patient's vital signs and institute supportive measures as indicated by the patient's clinical state. In particular, patients may require symptomatic treatment for cardiorespiratory effects or central nervous system effects.

Further absorption should be prevented using an appropriate method e.g. treatment within 1 - 2 hours with activated charcoal. If activated charcoal is used airway protection is imperative for drowsy patients.

If CNS depression is severe consider the use of flumazenil, a benzodiazepine antagonist. This should only be administered under closely monitored conditions. It has a short half-life (about an hour), therefore patients administered flumazenil will require monitoring after its effects have worn off. Flumazenil is to be used with extreme caution in the presence of medicines that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil, for further information on the correct use of this medicine.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacological classification: A 2.6 – Tranquilizers

Pharmacotherapeutic group: Pharmacotherapeutic group: benzodiazepines, ATC-code: N05BA01

Mechanism of action

Diazepam is a long-acting benzodiazepine hypnotic with anxiolytic, sedative, muscle-relaxant, anticonvulsant and amnesic properties.

Its action is enhanced by generation of active metabolites (mainly desmethyl-diazepam). The central actions of benzodiazepines are mediated through an enhancement of the GABAergic (Gamma-aminobutyric acid mediated) neurotransmission at inhibitory synapses. In the presence of benzodiazepines, the affinity of the GABA receptor for the neurotransmitter is enhanced through positive allosteric modulation resulting in an increased action of released GABA on the postsynaptic transmembrane chloride ion flux.

The major sites of action of diazepam on the spinal reflexes are supraspinal. However, this action is in part mediated by the brain stem reticular system. It depresses the duration of electrical after discharge in the limbic system, including the septal region, amygdala and hippocampus.

5.2. Pharmacokinetic properties

Absorption

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

Ampoules: On i.m. injection, absorption of diazepam is complete. The rate of absorption is variable and depends on site and depth of the injection.

Following daily dosing, diazepam levels reach a steady state within approximately 5 days; it takes about twice as long before desmethyl-diazepam levels reach a steady-state. 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.

During treatment, the elimination half-life of diazepam may increase by 50 % due to a reduction in hepatic clearance. Reports on the evolution of plasma levels during long-term treatment are conflicting. A strong decrease of diazepam levels during long-term treatment, possibly due to metabolic auto-induction, has been found, but in other studies plasma concentrations of both diazepam and its desmethyl metabolite were independent of duration of therapy.

Distribution

Diazepam is widely distributed into tissues despite high binding to plasma proteins (98 – 99 %), mainly albumin and to lesser extent α_1-acid glycoprotein. After intravenous administration, a pronounced distribution phase is seen in plasma concentrations with half-life of distribution of up to 3 hours.

The volume of distribution at steady state averages between 0,88 and 1,1 L/kg when derived from plasma concentration measurements. Both protein binding and volume of distribution of desmethyl-diazepam are similar to those of diazepam.

The high protein binding limits the extent of diazepam uptake into the cerebrospinal fluid (CSF). CSF levels in man following single and multiple doses approximate closely the free drug concentration in

plasma. Upon multiple dosing desmethyl-diazepam, but not diazepam, may significantly accumulate in CSF. Diazepam has very rapid uptake into and equilibration with brain tissue, with equilibrium concentrations in brain exceeding those in plasma. The overall time-course of receptor occupancy was consistent with the time-course of the sum of brain concentrations of diazepam plus metabolites.

Metabolism

Diazepam is mainly metabolised to pharmacologically active metabolites such as desmethyl-diazepam, a pathway accounting for 50 – 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.

Oxazepam and temazepam are further conjugated to glucuronides. After multiple doses of diazepam plasma concentration ratios of desmethyl-diazepam/ diazepam were 1,1 ± 0,2, temazepam/ diazepam 0,11 ± 0,05, and oxazepam/ diazepam 0,09 ± 0,03.

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. Because CYP2C19 is polymorphic, extensive metabolisers (EMs), and poor metabolisers (PMs) of diazepam can be distinguished. PMs of diazepam showed significantly lower clearance (12 vs 26 mL/min) and longer elimination half-life (88 vs 41 h) of diazepam than EMs after a single oral dose. Also, PMs had lower clearance, higher AUC and longer elimination half-life of desmethyl-diazepam. There appear to be inter-ethnic differences in this polymorphism.

Elimination

The decline in the plasma concentration-time profiles after oral and i.v. administration of diazepam is biphasic; an initial rapid and extensive distribution phase being followed by a prolonged terminal elimination phase. Typical terminal elimination half-life values are in the range of 24 - 48 hours for diazepam and 40 - 100 hours for the active metabolite desmethyl-diazepam. The clearance of diazepam is 20 – 40 mL/min. Only insignificant amounts of unchanged diazepam are eliminated indicating that the drug is almost completely metabolised before leaving the body. Oxazepam-glucuronide is the main drug-related product in urine.

Pharmacokinetics in special populations

Elderly Population

Benzodiazepine pharmacologic effects appear to be greater in elderly patients than in younger patients even at similar plasma benzodiazepine concentrations, possibly because of age-related changes in drug–receptor interactions, post-receptor mechanisms and organ function.

The unbound fraction of diazepam correlates positively with age and was higher in elderly than in young subjects. Age decreases the capacity of the liver for N-demethylation and 3-hydroxylation of diazepam. An age-dependent decrease in clearance of unbound drug occurs and is responsible for the observed 2 - 4-fold increase in elimination half-life in the elderly, with a stronger effect seen in males than females. Hence the extent of accumulation of unbound pharmacologically active diazepam in elderly persons during multiple dosing will be greater than in younger adults. The elimination of desmethyl-diazepam is slower in elderly males, but not in females.

Hepatic impairment

Disposition of both diazepam and desmethyl-diazepam is altered in liver disease. In acute viral hepatitis, the half-life of diazepam is increased by about 2-fold but returns slowly to normal on recovery. A more marked (2- to 5-fold) increase in the elimination half-life is seen in patients with alcoholic cirrhosis. These changes are primarily due to impaired hepatic metabolism; altered distribution due to changes in protein binding may be contributory. The reduced clearance of diazepam and desmethyl-diazepam leads to their increased accumulation during long-term dosing. This in turn is associated with increased sedation.

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 insufficiency and healthy individuals. Due to changes in plasma protein binding and tissue distribution of diazepam its elimination half-life was shortened in renal disease from (mean ± S.E.) 92 ± 23 h in control to 37 ± 7 h in renal failure subjects.

Pregnancy

Diazepam and desmethyl-diazepam readily cross the placental barrier. The foetus can also carry out N-demethylation of diazepam. Long-term treatment leads to accumulation of both compounds in the foetus with high levels in the foetal heart, lungs and brain.

Plasma protein binding of diazepam is decreased during pregnancy, particularly during the last trimester, partly due to the fall in serum albumin concentration. Increased pharmacological effects may result after acute dosing (see section 4.6).

Paediatric Population

During the first day of life, the free fractions of diazepam and desmethyl-diazepam increased sharply to twice the values at birth and subsequently declined slowly to reach near control values at one week of age. These changes parallel those of free fatty acid concentrations.

Newborns and premature infants metabolise diazepam more slowly than older children and adults leading to a prolonged half-life (very pronounced in premature newborns) unless there was exposure to inducing agents before or immediately after birth. The newborn's capacity to carry out metabolic processes involved in the biotransformation of diazepam, including hydroxylation, demethylation, and glucuronide conjugation, remains limited before 5 months of age; after this time hepatic enzymes develop to or even exceed adult capacity.

Diazepam and its metabolites are excreted in breast milk. Concentrations of diazepam in milk are only 10 % of those in maternal blood. Normalized for body weight, approximately 5 % of the mother’s dose reaches the baby. After multiple administrations of more than 10 mg daily doses the amounts transferred may be large enough to show effects in the baby (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablets:

Lactose monohydrate, maize starch, magnesium stearate, iron oxide yellow (VALIUM 5 mg), indigotine (VALIUM 10 mg).

Injection in Ampoules:

Benzyl alcohol, benzoic acid, sodium benzoate, ethyl alcohol, propylene glycol, sodium hydroxide and water for injection.

6.2. Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3. Shelf life

VALIUM 5 mg: 60 months

VALIUM 10 mg: 60 months

VALIUM 10 mg/2 mL: 36 months

Chemically and physically in use stability has been demonstrated for 24 hours at room temperature (25 °C). From a microbiological point of view VALIUM should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4. Special precautions for storage

Tablets: Store at or below 30 °C.

Ampoules: Store at or below 30 °C.

Keep out of reach and sight of children.

Keep ampoules and tablets in the outer carton until required for use.

6.5. Nature and contents of container

VALIUM 5 mg: 30's and 90's

VALIUM 10 mg: 30's and 90's

VALIUM 10 mg/2 mL: 5’s

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

VALIUM injection can be diluted with the following solutions: Sodium chloride 0,9 %; Glucose 5 % or Glucose 10 %.

Use of PVC-containing infusion sets

Use of PVC-containing containers and infusion sets may result in decreased concentrations of diazepam (see section 4.4).

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established "collection systems", if available in your location.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharmaco Distribution (Pty) Ltd.

3 Sandown Valley Crescent

South Tower, First Floor

Sandton 2196, Gauteng

South Africa

Ethical assistance Line: +27 (0)11 784 00 77

8. REGISTRATION NUMBER(S)

VALIUM 10 mg/2 mL injection: B/2.6/995

VALIUM 5 mg tablet: B/2.6/1003

VALIUM 10 mg tablet: B/2.6/1004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

8 April 1974 (injection); 9 March 1989 (tablets)

10. DATE OF REVISION OF THE TEXT

30 September 2025

VALIUM 10 mg/2 mL	
BOTSWANA Reg. No. B9308355	1C
NAMIBIA Reg. No. 90/2.6/001433	NS3

VALIUM 5 mg	
NAMIBIA Reg. No. 90/2.6/001436	NS3

VALIUM 10 mg	
NAMIBIA Reg. No. 90/2.6/001434	NS3