SCHEDULING STATUS

S5

PROPRIETARY NAME AND DOSAGE FORM

VALIUM® 5 mg tablet

VALIUM® 10 mg tablet

VALIUM® 10 mg/2 mℓ injection

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.

Inactives/Excipients:

Lactose monohydrate, maize starch, magnesium stearate, iron oxide yellow (VALIUM 5 mg), indigotine 85 % (VALIUM 10 mg). VALIUM tablets contain sugar (lactose).

Injection in Ampoules

Each ampoule contains 10 mg diazepam per 2 mℓ.

Inactives/Excipients:

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

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

PHARMACOLOGICAL CLASSIFICATION

A 2.6 - Tranquilizers

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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

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. These actions result from potentiation of the neural inhibition that is mediated by Gamma-aminobutyric acid (GABA).

Pharmacokinetic properties

Absorption

Ampoules: On i.m. injection, absorption of diazepam is complete.

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

Distribution

Diazepam and its metabolites are highly bound to plasma proteins (diazepam 98 %). Diazepam and its metabolites cross the blood-brain and placental barriers and are also found in breast milk. The volume of distribution at steady state is 0,8 - 1,0 ℓ/kg. The half-life of distribution is up to 3 hours.

Metabolism

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

The oxidative metabolism of diazepam is mediated by CYP3A and CYP2C19 isoenzymes.

Oxazepam and temazepam are further conjugated to glucuronic acid.

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 (half-life up to about 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 into the urine, predominantly in their conjugated forms. The clearance of diazepam is 20 - 30 mℓ/min.

Pharmacokinetics in special populations

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

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 assessed regularly and the need for continued treatment should be re-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 (including tetanus).

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: Refer Tablets above.

CONTRAINDICATIONS

VALIUM is contraindicated in patients with:

- a known history of hypersensitivity to benzodiazepines;
- severe respiratory insufficiency;
- severe hepatic insufficiency;
- 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 WARNINGS AND SPECIAL PRECAUTIONS).

WARNINGS AND SPECIAL PRECAUTIONS

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, clinically relevant respiratory and/or cardiovascular depression (See INTERACTIONS).

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 Medicine abuse and dependence below.

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

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

A lower dose is recommended for patients with chronic respiratory insufficiency, due to the risk of respiratory depression, (see CONTRAINDICATIONS). Lower doses should also be used for elderly and debilitated patients.

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 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.

Children

Since the safety and effectiveness in paediatric patients below the age of 6 months have not been established, VALIUM should be used in this age group with extreme caution and only when other therapeutic alternatives are not available.

Ampoules

VALIUM is adsorbed to plastic infusion bags and infusion sets 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. PVC-containing bags and infusion sets should be avoided when infusing VALIUM. 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.

Myasthenia gravis patients

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

Elderly and debilitated patients

Extreme care must be used when using VALIUM, particularly by the i.v. route, to the elderly, to 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.

Injection into very small veins and intra-arterial injection

Smaller 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.

Medicine abuse and dependence

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 these patients.

Withdrawal

Once physical dependence had developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headache, 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 epileptic seizures. 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.

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.

Duration of treatment

The duration of treatment should be as short as possible. (See DOSAGE AND DIRECTIONS FOR USE). The overall duration of treatment, generally, should not be more than 8 to 12 weeks, including the tapering-off process.

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 CONTRAINDICATIONS).

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 PREGNANCY AND LACTATION).

Lactose in VALIUM Tablets

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

Effects on the ability to drive and use machines

Sedation, amnesia, impaired concentration and impaired muscle function may adversely affect the ability to drive or operate machinery. Patients should be advised, particularly at the initiation of therapy, against taking charge of vehicles or machinery or performing potentially hazardous tasks where loss of concentration could lead to accidents.

INTERACTIONS

Pharmacodynamic Interactions

Enhanced effects of sedation, respiration, and haemodynamics may 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, or alcohol.

Concomitant use of barbiturates, alcohol or other central nervous system depressants increases cardiorespiratory depression with increased risk of apnoea.

Alcohol should be avoided in patients receiving VALIUM. (See WARNINGS AND SPECIAL PRECAUTIONS and KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT).

Pharmacokinetic Interactions

The oxidative metabolism of diazepam, leading to the formation of N-desmethyldiazepam, of 3 hydroxydiazepam (tenazepam) and of oxazepam, is mediated by CYP2C19 and CYP3A cytochrome P450 isoenzymes.

As shown by *in vitro* study, the hydroxylation reaction is carried out mainly by CYP3A isoform whereas the N-desmethylation is mediated by both CYP3A and CYP2C19.

Results from *in vivo* studies in human volunteers have confirmed the *in vitro* observations.

In consequence substrates, which are modulators of CYP3A and or of CYP2C19, may potentially alter the pharmacokinetics of diazepam. Medicines like cimetidine, ketoconazole, fluvoxamine, fluoxetine and omeprazole which are CYP3A or CYP2C19 inhibitors may lead to increased and prolonged sedation. 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.

PREGNANCY AND LACTATION

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. 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).

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

DOSAGE AND DIRECTIONS FOR USE

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 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 and the maximum dose should not be exceeded.

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 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.

Impaired hepatic or renal function:

Patients with impaired hepatic function should be given a reduced dose.

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

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.

Elderly and debilitated patients

Elderly patients and those with impaired hepatic function 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.

Special dosage instructions

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.

Special instructions for use, handling and disposal

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

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.

SIDE-EFFECTS

Tablets and Injection:

Frequent:

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

Psychiatric disorders

Less frequent:

Drowsiness, confusion, numbed emotions, depression, reduced alertness, increase or decrease in libido. 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. If these occur, VALIUM should be discontinued.

There is potential for abuse. Withdrawal symptoms (including convulsions) have occurred following abrupt cessation, especially in patients who have received large doses for prolonged periods.

Physical and psychic dependence, (see WARNINGS AND SPECIAL PRECAUTIONS).

Nervous system disorders

Less frequent:

Fatigue, headache, ataxia, dizziness, hypersalivation, slurred speech, dysarthria, tremor, numbed emotions, anterograde amnesia – (see WARNINGS AND SPECIAL PRECAUTIONS), reduced alertness, dry mouth, vertigo. VALIUM may increase the frequency and severity of attacks of grand mal epilepsy, during treatment or abrupt withdrawal.

Cardiac disorders

Less frequent:

Cardiac failure including cardiac arrest, variations in pulse rate. Cardio-respiratory depression may occur if VALIUM is administered rectally.

Vascular disorders

Less frequent:

Hypotension, variations in pulse rate, circulatory depression.

Respiratory, thoracic and mediastinal disorders

Less frequent:

Circulatory depression. Respiratory depression including respiratory failure due to a depressant effect on the respiratory centre and cardiovascular collapse, may occur following intravenous and intramuscular administration.

Eye disorders

Less frequent:

Diplopia, blurred vision

Gastrointestinal disorders

Less frequent:

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

Hepato-biliary disorders

Less frequent:

Elevated transaminases and alkaline phosphatase, jaundice.

Renal and urinary disorders

Less frequent:

Incontinence, urinary retention.

Skin and subcutaneous tissue disorders

Less frequent:

Skin reactions.

Ear and labyrinth disorders

Less frequent:

Vertigo.

Injury and poisoning

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.

Investigations

Less frequent:

Elevated transaminases and alkaline phosphatase.

Injection

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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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. VALIUMS 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.

IDENTIFICATION

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.

PRESENTATION

VALIUM 5 mg: 100's

VALIUM 10 mg: 100's

VALIUM 10 mg/2 mℓ: 5's

STORAGE INSTRUCTIONS

Tablets: Store at or below 30 °C.

Ampoules: Store at or below 30 °C.

Keep out of reach of children.

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

REGISTRATION NUMBERS

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

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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