Australian Product Information - VALIUM (diazepam)

1. NAME OF THE MEDICINE

Diazepam

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Valium tablet contains 5 mg diazepam.

Excipients with known effect: contains sugars as lactose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

Valium 5 mg tablets are cylindrical, biplanar, yellow tablet, upper face marked V 5, lower face scored.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Valium is indicated for the management of anxiety disorders or for the short term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

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

Valium is a useful adjunct for the relief of reflex muscle spasm due to local trauma (injury, inflammation) to muscles, bones and joints. It can also be used to combat spasticity due to upper motor neuron lesions such as cerebral palsy and paraplegia, as well as in athetosis and stiff-man syndrome.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

For maximal beneficial effect, the dosage should be carefully individualised. Dosage may need to be reduced in patients with hepatic or renal disease as the elimination half-life may be prolonged in this sub-group.

Usual Adult Dosage

5 - 40 mg daily.

Average dosage for ambulatory patients

2 mg three times daily or 5 mg in the evening and 2 mg once or twice during the day.

Elderly or debilitated patients

2 mg twice daily or half the usual adult dose.

Children

6 months to 3 years

1 - 6 mg daily.

4 to 14 years

4 - 12 mg daily or calculated from 0.1 - 0.3 mg/kg bodyweight.

Hospital treatment of tension, excitation, motor unrest

10 - 15 mg three times daily until the acute symptoms subside.

Muscle spasm

10 - 30 mg daily.

Special populations

Elderly patients

Elderly patients should be given a reduced 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.

Paediatric patients

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

Hepatic impairment

Valium is contraindicated in patients with severe hepatic impairment (see Section 4.3 CONTRAINDICATIONS). Caution should be exercised when administering Valium to patients with mild to moderate hepatic impairment. If treatment is necessary, it is recommended to initiate Valium at the lowest dose possible and to increase the dosage only to the extent that such an increase is compatible with the degree of residual hepatic function. If administered for protracted periods, such patients should be monitored closely and have periodic liver function tests.

Renal impairment

If treatment is necessary in patients with impaired renal function, it is recommended to initiate Valium at a very low dose, and if required, increase the dose carefully and gradually. If Valium is administered for protracted periods, such patients should be monitored closely.

4.3 CONTRAINDICATIONS

Valium is contraindicated in patients with:

- known hypersensitivity to benzodiazepines, diazepam or any of the excipients
- chronic obstructive pulmonary disease with incipient respiratory failure.

Oral Valium is also contraindicated in patients with:

- severe respiratory insufficiency
- severe hepatic impairment as benzodiazepines may precipitate hepatic encephalopathy
- sleep apnoea syndrome
- myasthenia gravis
- dependence on CNS depressants including alcohol. An exception to the latter is the management of acute withdrawal reactions.

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

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Concomitant use of alcohol/CNS depressants

Patients should be advised that their tolerance for alcohol and other CNS depressants (including anxiolytics, sedatives, antidepressants including tricyclic anti-depressants and non-selective MAO inhibitors, sedative antihistamines, opioids and anaesthetics) will be diminished and that these medications should either be eliminated or given in reduced dosage in the presence of Valium. 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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Tolerance

In general, benzodiazepines should be prescribed for short periods only (e.g. 2 - 4 weeks). Continuous long-term use of Valium is not recommended. There is evidence that tolerance develops to the sedative effects of benzodiazepines. After as little as one week of therapy, withdrawal symptoms can appear following the cessation of recommended doses (e.g. rebound insomnia following cessation of a hypnotic benzodiazepine).

Tolerance, as defined by a need to increase the dose in order to achieve the same therapeutic effect, seldom occurs in patients receiving recommended doses under medical supervision. Tolerance to sedation may occur with benzodiazepines, especially in those with drug seeking behaviour.

Following the prolonged use of Valium at therapeutic doses, withdrawal from the medication should be gradual. An individualised withdrawal timetable needs to be planned for each patient in whom dependence is known or suspected. Periods from 4 weeks to 4 months have been suggested. As with other benzodiazepines, when treatment is suddenly withdrawn, a temporary increase in sleep disturbance can occur after use of Valium (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Drug abuse and dependence).

Drug abuse and dependence

Dependence

Use of benzodiazepines and benzodiazepine-like agents may lead to the development of physical and psychological dependence (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)), as defined by the presence of a withdrawal syndrome on discontinuation of the drug. The risk of dependence increases with dose and duration of treatment. It is more pronounced in patients on long-term therapy and/or high dosage and particularly so in predisposed patients with a history of alcohol or drug abuse. Abuse has been reported in poly-drug abusers. Valium should be used with extreme caution in patients with a history of alcohol or drug abuse.

Withdrawal

When benzodiazepines are used, withdrawal symptoms may develop when switching to a benzodiazepine with a considerably shorter half-life.

Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol, have occurred once physical dependence to benzodiazepines has developed or following abrupt discontinuation of benzodiazepines. They may consist of headache, diarrhoea, muscle pain, insomnia, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases, the following symptoms may occur: dysphoria, palpitations, panic attacks, vertigo, myoclonus, akinesia, hypersensitivity to light, sound and touch, abnormal body sensations (e.g. feeling of motion, metallic taste), depersonalisation, derealisation, delusional beliefs, hyperreflexia and loss of short term memory, to a major syndrome which may include convulsions, tremor, abdominal and muscle cramps, confusional state, delirium, hallucinations, hyperthermia, psychosis, vomiting and sweating.

Such manifestations of withdrawal, especially the more serious ones, are more common in patients who have received excessive doses over a prolonged period. However, withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines taken continuously at therapeutic levels. Accordingly,

Valium should be terminated by tapering the dose to minimise occurrence of withdrawal symptoms. Patients should be advised to consult with their physician before either increasing the dose or abruptly discontinuing the medication.

Rebound phenomena have been described in the context of benzodiazepine use. Rebound insomnia and anxiety mean an increase in the severity of these symptoms beyond pre-treatment levels following cessation of benzodiazepines. Rebound phenomena in general possibly reflect re-emergence of pre-existing symptoms combined with withdrawal symptoms described earlier. Some patients prescribed benzodiazepines with very short half-lives (in the order of 2 to 4 hours) may experience relatively mild rebound symptoms in between their regular doses. Withdrawal/rebound symptoms may follow high doses for relatively short periods.

Rebound anxiety

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

Lactose intolerance

Since Valium contains lactose, patients with rare hereditary problems of galactose intolerance (the Lapp lactase deficiency or glucose-galactose malabsorption) should not take this medicine.

Hypotension

Although hypotension has occurred rarely, Valium should be administered with caution to patients in whom a drop in blood pressure might lead to cardiac or cerebral complications. This is particularly important in elderly patients.

Amnesia

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines. Anterograde amnesia may occur using therapeutic dosages: the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour

Acute narrow-angle glaucoma

Caution should be used in the treatment of patients with acute narrow-angle glaucoma (because of atropine-like side effects).

Use in hepatic impairment

Benzodiazepines may have a contributory role in precipitating episodes of hepatic encephalopathy in severe hepatic impairment (see Section 4.3 CONTRAINDICATIONS).

Special caution should be exercised when administering Valium to patients with mild to moderate hepatic impairment (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

As with other benzodiazepines, periodic liver function tests are recommended.

Use in renal impairment

Patients with impaired renal function should use benzodiazepine medication with caution and dosage reduction may be advisable (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Blood dyscrasias

In rare instances, some patients taking benzodiazepines have developed blood dyscrasias, as with other benzodiazepines, periodic blood counts are recommended.

Depression, psychosis and schizophrenia

Valium is not recommended as primary therapy in patients with depression and/or psychosis. In such conditions, psychiatric assessment and supervision are necessary if benzodiazepines are indicated.

Benzodiazepines may increase depression in some patients and may contribute to deterioration in severely disturbed schizophrenics with confusion and withdrawal. Suicidal tendencies may be present or uncovered and protective measures may be required.

Psychiatric and paradoxical reactions

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, anxiety, anger, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects, acute rage, stimulation or excitement may occur. Should such reactions occur, Valium should be discontinued. They are more likely to occur in children and in the elderly.

Respiratory insufficiency

Caution in the use of Valium is recommended in patients with respiratory depression. In patients with chronic obstructive pulmonary disease, benzodiazepines can cause increased arterial carbon dioxide tension and decreased oxygen tension.

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

Epilepsy

When Valium is administered to persons with convulsive disorders, an increase in the frequency and/or severity of grand mal seizures may occur, necessitating increased anticonvulsant medication. Abrupt withdrawal of benzodiazepines in persons with convulsive disorders may be associated with a temporary increase in the frequency and/or severity of seizures.

Medical history of alcohol or drug abuse

Extreme caution must be exercised in administering Valium to individuals with a history of alcohol or drug abuse, dependence on CNS depressants, those known to be addiction prone, or those whose history suggests they may increase the dosage on their own initiative. It is desirable to limit repeat prescription without adequate medical supervision.

Use in the elderly

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 (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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

Elderly or debilitated patients may be particularly susceptible to the sedative effects of benzodiazepines and associated giddiness, ataxia and confusion, which may increase the risk of a fall.

Lower doses should be used for elderly and debilitated patients.

Paediatric Use

Prolonged central nervous system depression has been observed in neonates due to inability to transform the drug. In view of lack of adequate clinical experience, oral use is not recommended in children younger than 6 months.

Effects on laboratory tests

Minor EEG changes, usually low voltage fast activity, of no known clinical significance have been reported with benzodiazepine administration.

Diazepam can inhibit binding of thyroxine and liothyronine to their binding proteins resulting in erroneously abnormal values from thyroid function test.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Pharmacokinetic drug-drug-interactions (DDI)

The metabolism of diazepam and its main metabolite, desmethyldiazepam depends on the cytochrome P450 isozymes CYP3A4 and CYP2C19. Modulators of these enzymes may lead to changes in diazepam disposition and effects. Stronger interactions are seen with compounds that affect more than one of diazepam's oxidative metabolic pathways. Inhibitors of CYP3A4 and CYP2C19 decrease metabolic rate and may lead 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 drugs 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 drugs on the pharmacokinetics of diazepam

Enzyme inhibitors

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. This may result in excessive or prolonged sedation. Patients should be advised to avoid grapefruit juice while taking diazepam.

Antimycotic azole derivatives inhibit CYP3A4 and CYP2C19 pathways and lead to increased exposure to diazepam. In a clinical trial using a single dose of 5 mg diazepam, fluconazole increased the AUC of diazepam 2.5-fold and prolonged elimination half-life from 31 h to 73 h, while voriconazole increased the AUC of diazepam 2.2-fold and prolonged elimination half-life from 31 h to 61 h. In another clinical trial using a single dose of 5 mg diazepam, itraconazole had a more moderate effect (AUC increased by 15%, elimination half-life prolonged from 26.5 to 35.5 h). The increased exposure to diazepam may result in greater and more prolonged sedation. Therefore, it is recommended to avoid concomitant use of these drugs (including ketoconazole) with diazepam or reduce the dose of diazepam.

The serotonin reuptake inhibitor fluvoxamine also inhibits both of diazepam's CYP3A4 and CYP2C19 degradation pathways. In a clinical trial using a single dose of 10 mg diazepam, fluvoxamine increased not only the AUC of diazepam 3-fold 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 is a moderate inhibitor of CYP3A4. Fluoxetine showed a more moderate effect on diazepam AUC (approximately 50% increase) and did not affect psychomotor response because combined concentrations of diazepam and desmethyldiazepam were similar with and without fluoxetine. Fluvoxamine and fluoxetine may lead to increased and prolonged sedation. For patients taking fluvoxamine, a benzodiazepine metabolised via a non-oxidative pathway is recommended. Patients receiving fluoxetine with diazepam should be monitored closely.

Combined hormonal contraceptives appear to reduce the clearance (by 40%) 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. Monitor the clinical response to diazepam in women taking concomitant oral contraception. There is some limited evidence that benzodiazepines can increase the incidence of break-through bleeding in women with hormonal contraceptives.

The proton pump inhibitor omeprazole, a CYP2C19 and CYP3A4 inhibitor, administered at a dose of 20 mg daily increased the diazepam AUC by 40% and the half-life by 36%; at a dose of 40 mg daily, omeprazole increased the diazepam AUC by 122% and the half-life by 130%. The elimination of desmethyldiazepam was reduced as well. The effect of omeprazole was 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. Patients administering these drugs with diazepam should be monitored closely and the dose of diazepam should be reduced if necessary.

The histamine H2-receptor antagonist cimetidine, an inhibitor of multiple CYP isozymes, including CYP3A4 and CYP2C19, reduces the clearance of diazepam and of desmethyldiazepam by 40 to 50%. This 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. Therefore, when used with cimetidine, a reduction in the dose of diazepam may be necessary. Ranitidine and famotidine do not affect the hepatic elimination of diazepam.

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.

Antituberculosis therapy may change the disposition of diazepam. In the 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. When used with isoniazid, monitor patients and reduce the dose of diazepam if necessary.

The calcium channel blocker diltiazem, a substrate for the same CYP isozymes as diazepam and an inhibitor of CYP3A4, increased AUC (by approximately25%) 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 desmethyldiazepam also tended to increase. Exercise caution when using diazepam with diltiazem, irrespective of CYP2C19 metaboliser status.

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.

The psychostimulants modafinil and armodafinil induce CYP3A4 and inhibit CYP2C19; they may prolong the elimination of diazepam and cause excessive sedation. When used with these psychostimulants, monitor patients and reduce the dose of diazepam if necessary.

The use of other CYP3A or CYP2C19 inhibitors (such as clarithromycin, erythromycin, ritonavir and verapamil) with diazepam may lead to increased and prolonged sedation.

Enzyme inducers

Rifampicin potently induces CYP3A4 and also has a significant accelerating effect on the CYP2C19 pathway. When dosed at 600 mg daily for 7 days, diazepam 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. Diazepam should only be used together with rifampicin if no therapeutic alternative exists.

Carbamazepine is a known inducer of CYP3A4 and accelerated elimination (increased clearance, reduced half-life) of diazepam 3-fold while increasing concentrations of desmethyldiazepam. This can result in a reduced effect of diazepam.

Food, Antacids and Drugs affecting gut motility

Food 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.

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 drugs increase the rate of diazepam absorption, potentially resulting in a transient increase in sedation.

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

Narcotics (morphine, pethidine) decrease the absorption rate and lower peak concentrations of orally administered diazepam. However, due to the additive CNS depressant effect, the concomitant use of diazepam and opioids should be avoided (see Pharmacodynamic Drug- Drug Interaction (DDI) below).

If a decision is made to prescribe Valium concomitantly with opioids, prescribe the lowest effective dose and minimum duration of concomitant use. Follow patients closely for signs and symptoms of respiratory depression and sedation (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.9 OVERDOSE).

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

Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the opioid have been determined (see Section 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES).

Effect of diazepam on the pharmacokinetics of other drugs

Diazepam has not been found to induce or inhibit metabolising enzymes. Nevertheless, some interactions with other drugs occur where diazepam is the precipitant.

Phenytoin therapy was associated with higher concentrations and increased phenytoin intoxication when combined with diazepam in some but not all studies. Monitoring of serum levels of phenytoin is recommended when initiating or discontinuing diazepam.

Pharmacodynamic Drug-Drug Interaction (DDI)

Alcohol should be avoided in patients receiving Valium (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Concomitant use with alcohol is not recommended due to enhancement of the sedative effect.

See Section 4.9 OVERDOSE for warning of other central nervous system depressants including alcohol.

Enhanced side effects such as sedation and cardio-respiratory depression may also occur when Valium is co-administered with any centrally acting depressants including alcohol.

There are several reports of severe hypotension, cardiorespiratory depression, excessive sedation or loss of consciousness in patients receiving combined treatment with clozapine and benzodiazepines, including diazepam. Concomitant use of diazepam and clozapine is not recommended.

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

There are several reports of excessive sedation, loss of consciousness, severe hypotension, or cardiorespiratory depression sometimes resulting in death in patients receiving combined treatment with intramuscular olanzapine and benzodiazepines, including diazepam. Concomitant parenteral use is not recommended.

When combined with methadone diazepam may enhance euphoria, leading to an increased risk of abuse or dependence. Diazepam increased the subjective and sedative opioid effects of methadone in a manner that

may heighten abuse potential. A significantly greater deterioration in reaction time was observed compared to methadone alone.

Reversible loss of control of Parkinson's disease has been seen in some patients treated with combined levodopa and diazepam.

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

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.

The anti-cholinergic effects of other drugs including atropine and similar drugs, anti-histamines and anti-depressants may be potentiated.

Interactions have been reported between some benzodiazepines and anti-convulsants (e.g., diazepam with phenytoin or with carbamazepine), with changes in the serum concentration of the benzodiazepine or anti-convulsant. It is recommended that patients be observed for altered responses when benzodiazepines and anti-convulsants are prescribed together and that serum level monitoring of the anti-convulsant is performed more frequently.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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 (22-fold the MRHD on a body surface area basis) to both males and females prior to and during mating and throughout gestation and lactation. No adverse effects were observed at 10 mg/kg/day (60 mg/m2/day, twice the MRHD).

Use in pregnancy

Category C

The safety of Valium for use in human pregnancy has not been established. Diazepam and its metabolites readily cross the placenta. An increased risk of congenital malformation associated with the use of benzodiazepines during the first trimester of pregnancy has been suggested. Benzodiazepines should be avoided during pregnancy unless there is no safer alternative.

Benzodiazepines cross the placenta and may cause hypotension, hypotonia, reduced respiratory function and hypothermia in the newborn infant.

Continuous treatment during pregnancy and administration of high doses in connection with delivery should be avoided. Withdrawal symptoms in newborn infants have been reported with this class of drugs. Special care must be taken when Valium is used during labour and delivery, as single high doses may produce irregularities in the foetal heart rate and hypotonia, poor sucking, hypothermia and moderate respiratory depression (floppy infant syndrome) in the neonate. With newborn infants it must be remembered that the enzyme system involved in the breakdown of the drug is not yet fully developed (especially in premature infants).

Diazepam was found to be teratogenic in mice at intravenous doses of 45 mg/kg or greater and oral doses of 100 mg/kg or greater (both 10-fold the MRHD on a body surface area basis), as well as in hamsters at 280 mg/kg (41-fold the MRHD). The respective no-effect doses were 50 mg/kg (5-fold the MRHD) in mice and 200 mg/kg (30-fold the MRHD) in hamsters. Malformations included exencephaly, cranioschisis, kinking of the spinal cord, and cleft palate with and without cleft lip. Malformations were not observed in rats or rabbits at respective doses of up to 300 and 50 mg/kg/day (greater than 20-fold the MRHD). Delayed development has been reported in offspring from several animal species treated with diazepam during pregnancy or during pregnancy and lactation.

Use in lactation

Valium is excreted in human breast milk and may cause drowsiness and feeding difficulties in the infant. Breast-feeding is not recommended in patients receiving oral Valium.

Females and males of reproductive potential

A woman of childbearing potential should contact her physician regarding the discontinuation of Valium if she intends to become pregnant 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 operate dangerous machinery or motor vehicles until completely recovered. The physician should decide when these activities may be resumed. Abilities may be impaired on the day following use.

If sleep duration is insufficient or alcohol and/or other CNS depressant drugs are consumed, the likelihood of impaired alertness may be increased (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most commonly reported undesirable effects are fatigue, drowsiness, muscle weakness, and ataxia; they are usually dose-related.

Nervous System Disorders: Ataxia, dysarthria, slurred speech, headache, tremor, dizziness, decreased alertness. Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour.

Psychiatric Disorders: Paradoxical reactions such as restlessness, acute disorientation, aggressiveness, nervousness, hostility, anxiety, delusion, anger, nightmares, abnormal dreams, hallucinations, psychoses, hyperactivity, inappropriate behaviour and other adverse behavioural effects are known to occur. Should these occur, use of the drug should be discontinued. They are more likely to occur in children and in the elderly.

Confusional state, emotional and mood disturbances, depression, changes 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 phenomena (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Abuse of benzodiazepines has been reported (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Injury, Poisoning and Procedural Complications: 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, dry mouth or hypersalivation, constipation and other gastrointestinal disturbances.

Eye Disorders: Diplopia, vision blurred.

Vascular Disorders: Hypotension, circulatory depression.

Investigations: Irregular heart rate, very rarely increased transaminases, increased blood alkaline phosphatase.

Renal and Urinary Disorders: Incontinence, urinary retention.

Skin and Subcutaneous Tissue Disorders: Skin reactions, such as rash.

Ear and Labyrinth Disorders: Vertigo.

Cardiac Disorders: Cardiac failure including cardiac arrest.

Respiratory Disorders: Respiratory depression including respiratory failure.

Hepatobiliary Disorders: Very rarely jaundice.

Haemopoietic Disorders: Isolated instances of neutropenia

Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, dysarthria, nystagmus, mental confusion and lethargy. In more serious cases, symptoms may include ataxia, areflexia, hypotonia, hypotension, apnoea, cardiorespiratory depression, coma and very rarely death. Coma may be more protracted and cyclical, particularly in elderly patients. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease.

Benzodiazepines increase the effects of other central nervous system depressants, including alcohol. When combined with other CNS depressants, the effects of overdosage are likely to be severe and may prove fatal.

Treatment

Treatment of overdosage is symptomatic; institute supportive measures as indicated by the patient's clinical state. If the overdosage is known to be small, observation of the patient and monitoring of their vital signs only may be appropriate. In adults or children who have taken an overdose of benzodiazepines within 1 - 2 hours, consider activated charcoal with airway protection if indicated.

If CNS depression is severe consider the use of flumazenil (Anexate®), 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 may precipitate seizures and is to be used with extreme caution in the presence of drugs that reduce seizure threshold (e.g. tricyclic antidepressants) and epileptic patients who have been treated with benzodiazepines. Refer to the prescribing information for flumazenil (Anexate®), for further information on the correct use of this drug.

Haemoperfusion and haemodialysis are not useful in benzodiazepine intoxication.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Diazepam is a member of the group of classical benzodiazepines and exhibits anxiolytic, sedative, muscle relaxant and anticonvulsant effects. Its action is enhanced by generation of active metabolites (mainly desmethyldiazepam). The central actions of benzodiazepines are mediated through enhancement of the GABAergic 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.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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

Following daily dosing, diazepam levels reach a steady state within approximately 5 days; it takes about twice as long before desmethyldiazepam 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 in 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 a lesser extent α1-acid glycoprotein). After intravenous administration, a pronounced distribution phase is seen in plasma concentrations with a 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 desmethyldiazepam 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 desmethyldiazepam, 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 metabolised to pharmacologically active metabolites such as desmethyldiazepam, 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.

Oxidation of diazepam is mediated by cytochrome P450 isozymes; formation of desmethyldiazepam 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 desmethyldiazepam. There appear to be inter-ethnic differences in this polymorphism.

EliminationThe plasma concentration-time curve of diazepam is biphasic; an initial rapid and extensive distribution phase being followed by a prolonged terminal elimination phase. Typical elimination half-life values are in the range of 24 - 48 hours for diazepam and 40 - 100 hours for the active metabolite desmethyldiazepam. 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 patients

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 desmethyldiazepam is slower in elderly males, but not in females.

Hepatic impairment

Disposition of both diazepam and desmethyldiazepam 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 desmethyldiazepam 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 desmethyldiazepam readily cross the placental barrier. The fetus can also carry out N-demethylation of diazepam. Long-term treatment leads to accumulation of both compounds in the fetus with high levels in the fetal 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 FERTILITY, PREGNANCY AND LACTATION).

Paediatric patients

During the first day of life, the free fractions of diazepam and desmethyldiazepam 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 10% of those in maternal blood. Normalised for body weight, approximately 5% of the mother's dose reaches the baby. The amounts transferred may be large enough to show effects in the baby (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Limited data from a number of studies have provided weak evidence of a genotoxic potential Diazepam has been shown to induce aneuploidy in sperm obtained from both mice and humans treated with approximately 10 mg/m^2/day (less than the MRHD).

Carcinogenicity

The carcinogenic potential of oral diazepam has been studied in several rodent species. An increase in the incidence of malignant hepatocellular tumours occurred in male rats and mice following lifetime dietary administration of diazepam at 75 mg/kg/day (17- and 8-fold the MRHD on a body surface area basis, respectively). This was not observed in female rats and mice treated with 75 mg/kg/day or hamsters treated with 120 mg/kg/day (18-fold the MRHD).

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose monohydrate

Maize starch

Iron oxide yellow CI77492

Magnesium stearate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30 °C

6.5 NATURE AND CONTENTS OF CONTAINER

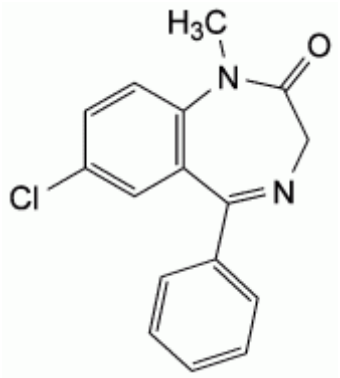
Valium 5mg tablets are available in a blister pack of 50 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Valium (diazepam) is a benzodiazepine derivative developed through original Roche research. Chemically, diazepam is 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. It is a colourless crystalline compound, insoluble in water and has a molecular weight of 284.74.

CAS number

439-14-5

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription only medicine

8. SPONSOR

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9. DATE OF FIRST APPROVAL

18 August 1994

10. DATE OF REVISION

11 February 2022

Summary table of changes

Section changed	Summary of new information
2	Revisions of excipients of known effect
3	Update to tablet description
8	PI reformat Sponsor updated to Atnahs Pharma (transferred from Roche)
All	Editorial changes