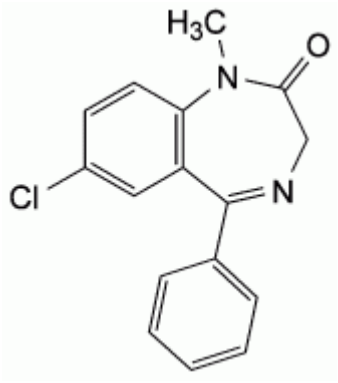
NAME OF THE MEDICINE

VALIUM

(*diazepam*)

CAS Registry Number: 439-14-5



DESCRIPTION

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.

PHARMACOLOGY

Pharmacodynamics

Mechanism of Action
Diazepam is a member of the group of classical benzodiazepines and exhibits anxiolytic, sedative, muscle relaxant and anti-convulsant effects. This is presumed to be the result of facilitating the action in the brain of gamma-aminobutyric acid, a naturally occurring inhibitory transmitter.

Pharmacokinetics

Absorption and Bioavailability
After oral administration, diazepam is rapidly and completely absorbed from the gastrointestinal tract, with peak plasma concentrations appearing 30 - 90 minutes after oral intake. The speed of onset after intramuscular (IM) administration is variable, depending on the muscle mass used and other factors.

Distribution
Diazepam is 98% protein-bound in the plasma, and is excreted in the urine mainly in the form of free or conjugated metabolites. VALIUM and its metabolites cross the blood-brain and placental barriers and are also found in breast-milk.

Metabolism
VALIUM is metabolised to hydroxy-diazepam (temazepam) and nordiazepam (t½ approximately 96 hours) and ultimately to oxazepam.

Elimination
The plasma concentration-time curve of VALIUM is biphasic; an initial rapid and extensive distribution phase with a half-life of up to 3 hours, followed by a prolonged terminal elimination phase (half-life 20 - 48 hours). The elimination half-life is 90 hours at age 80 and is increased 2 - 3-fold in patients with cirrhosis.

Pharmacokinetics in Special Populations
The elimination half-life may be prolonged in the newborn, the elderly and patients with hepatic or renal disease and it should be noted that the plasma concentration may take correspondingly longer to reach steady state.

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.

Intravenous VALIUM is useful in controlling status epilepticus and the spasms of tetanus.

CONTRAINDICATIONS

VALIUM is contraindicated in patients with:

- known hypersensitivity to benzodiazepines
- chronic obstructive pulmonary disease with incipient respiratory failure.

Oral VALIUM is also contraindicated in patients with:

- severe respiratory insufficiency
- severe hepatic insufficiency
- 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.

PRECAUTIONS

Patients should be advised that their tolerance for alcohol and other CNS depressants will be diminished and that these medications should either be eliminated or given in reduced dosage in the presence of VALIUM.

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).

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 **PRECAUTIONS Dependence**).

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.

Injectable VALIUM may increase the muscle weakness in myasthenia gravis and should be used with caution in this condition.

Very small veins should not be selected for injectable VALIUM. 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.

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).

Impairment of Fertility

Reproductive studies in rats showed decreases in the number of pregnancies and in the number of surviving offspring following administration of oral doses of 100 mg/kg/day (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/m^2/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).

Use in Lactation

VALIUM is excreted in human breast milk and may cause drowsiness and feeding difficulties in the infant. Since diazepam passes into breast milk, injectable VALIUM should not be administered to breast-feeding mothers. Breast-feeding is not recommended in patients receiving oral VALIUM.

Paediatric Use

Efficacy and safety of parenteral VALIUM has not been established in the neonate (30 days or less in age). Prolonged central nervous system depression has been observed in neonates due to inability to transform the drug. The benzyl alcohol contained in VALIUM ampoules may lead to irreversible damage in the newborn, especially in the premature. Therefore, for these patients the ampoules should only be used if no therapeutic alternative is available. In view of lack of adequate clinical experience, chronic oral use is not recommended in children younger than 6 months.

Use in Elderly or Debilitated Patients

An increased risk of falls and fractures has been recorded in elderly benzodiazepine users.

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.

Extreme care must be used in administering injectable 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 may occur. Concomitant use of barbiturates, alcohol, or other central nervous system depressants increases depression with increased risk of apnoea.

Lower doses should be used for elderly and debilitated patients.

Impaired Renal/Liver Function and Blood Dyscrasias

Patients with impaired renal or hepatic function should use benzodiazepine medication with caution and dosage reduction may be advisable. In rare instances, some patients taking benzodiazepines have

developed blood dyscrasias, and some have had elevation of liver enzymes. As with other benzodiazepines, periodic blood counts and liver function tests 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.

Paradoxical Reactions

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, 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.

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).

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).

Teratogenicity

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.

Impaired Respiratory Function

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 anti-convulsant 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.

Abuse

Extreme caution must be exercised in administering VALIUM to individuals with a history of alcohol or drug abuse, 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.

Dependence

The use of benzodiazepines may lead to dependence, 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. 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.

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. These symptoms range from insomnia, anxiety, 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.

Interaction with Other Medicines

The benzodiazepines, including VALIUM, produce additive CNS depressant effects when co-administered with other medications, which themselves produce CNS depression (e.g. barbiturates, alcohol, anxiolytics, sedatives, anti-depressants including tricyclic anti-depressants and non-selective MAO inhibitors, hypnotics, anti-epileptic drugs, phenothiazines and other anti-psychotics, skeletal muscle relaxants, anti-histamines, narcotic analgesics and anaesthetics). Therefore, it should be borne in mind that the effect of these drugs may potentiate or be potentiated by the action of VALIUM.

Concomitant use with alcohol is not recommended due to enhancement of the sedative effect.

There is a potentially relevant interaction between diazepam and compounds that inhibit certain hepatic enzymes (particularly cytochrome P 450 3A). Data indicate that these compounds influence the pharmacokinetics of diazepam and may lead to increased and prolonged sedation. VALIUM undergoes oxidative metabolism and, consequently, may interact with disulfiram, cimetidine, ketoconazole, fluvoxamine, fluoxetine or omeprazole resulting in increased plasma levels of VALIUM. Patients should be observed closely for evidence of enhanced benzodiazepine response during concomitant treatment with either disulfiram or cimetidine; some patients may require a reduction in benzodiazepine dosage.

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.

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, 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.

Effects on Laboratory Tests

Intramuscular injection (but not oral or *i.v.* administration) may lead to a rise in serum creatinine phosphokinase activity, with a maximum between 12 and 24 hours after injection. This fact should be taken into account in the differential diagnosis of myocardial infarction.

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.

Ability to Drive and Use Machines

Sedation, amnesia, impaired concentration and impaired muscle function may adversely affect the ability to drive or operate machinery. As with all patients taking CNS depressant medications, patients receiving VALIUM should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from VALIUM therapy. Abilities may be impaired on the day following use.

ADVERSE EFFECTS

Most commonly reported undesirable effects are fatigue, drowsiness, muscle weakness and ataxia; they are usually dose-related. Effects encountered infrequently are amnesia, confusion, constipation, depression, diplopia, dysarthria, gastrointestinal disturbances, headache, hypotension, incontinence, increase or decrease in libido, nausea, dry mouth or hypersalivation, skin reactions such as rash, slurred

speech, tremor, urinary retention, vertigo and blurred vision. Very rarely, elevated transaminases and alkaline phosphatase, jaundice as well as cases of cardiac arrest have been observed. Isolated instances of neutropenia have been seen.

Numbed emotion, reduced alertness, variations in pulse rate and circulatory depression have been reported occasionally with injectable VALIUM. Dizziness has been reported occasionally with oral VALIUM.

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

Paradoxical reactions such as acute hyperexcitation, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued.

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

Venous thrombosis, phlebitis, local irritation, swelling, or less frequently, vascular changes may occur, particularly after rapid IV injection. Intramuscular. injection can result in local pain, in some cases accompanied by erythema at the site of injection. Tenderness is relatively common.

DOSAGE AND ADMINISTRATION

Oral

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.

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.

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.

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

Parenteral

Note. Intravenous injection should be given into a large lumen vessel, such as an antecubital vein, and the solution should be administered slowly (1 mL, i.e. 5 mg per minute). Rapid injection or use of veins with too small a lumen carries the risk of syncope, hypotension, apnoea and thrombophlebitis. Resuscitation equipment must be kept ready at all times. Intra-arterial injection must be carefully avoided on account of the danger of necrosis. The IM route should be avoided if practicable because of variable absorption.

Lower doses should be used in the elderly, those with impaired hepatic function or debilitated patients. 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.

Adults

Moderate psychoneurotic reactions. Manifested by tension - anxiety, agitation, restlessness and psychophysiological disturbances: 2 - 5 mg IV or IM. Repeat in 3 - 4 hours if necessary.

Severe psychoneurotic reactions. Where severe anxiety, apprehension or agitation exist 5 - 10 mg IV or IM. Repeat in 3 - 4 hours if necessary.

Acute alcohol withdrawal. As an aid in symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis: 10 mg IV or IM initially, then 5 - 10 mg in 3 - 4 hours if necessary.

Endoscopic procedures. Adjunctively, if apprehension, anxiety or acute stress reactions are present prior to endoscopic procedures. Dosage of narcotics should be reduced by at least a third and in some cases may be omitted. Titrate IV dosage to desired sedative response such as slurring of speech, with slow administration immediately prior to the procedure. Generally, 10 mg or less is adequate, but up to 20 mg IV may be given, particularly when concomitant narcotics are omitted. If IV route cannot be used, give 5 - 10 mg IM approximately 30 minutes prior to the procedure.

Muscle spasm. Associated with local pathology, cerebral palsy, athetosis, stiff-man syndrome or tetanus: 5 - 10 mg initially IM or IV, then 5 - 10 mg in 3 - 4 hours if necessary. For tetanus larger doses may be required.

Status epilepticus and severe recurrent convulsive seizures. In the convulsing patient, the IV route is preferred. This injection should be administered slowly. However, if IV administration is impossible, the IM route may be used. Give 5 - 10 mg initially (IV preferred). This injection may be repeated if necessary at 10 - 15 minute intervals up to a maximum dose of 30 mg. If necessary, therapy with VALIUM may be repeated in 2 - 4 hours; caution must be exercised in individuals with chronic lung disease or unstable cardiovascular status.

Pre-operative medication. To relieve anxiety and tension (if atropine, hyoscine or other pre-medications are desired, they must be administered in separate syringes): 10 mg IM before surgery.

Cardioversion. To relieve anxiety and tension and to reduce recall of procedure: 5 - 15 mg IV within 5 - 10 minutes prior to procedure.

Children

Intravenous administration should be made slowly.

Muscle spasm. For tetanus in infants over 30 days of age: 1 - 2 mg IM or IV, slowly repeated every 3 - 4 hours as necessary. In children 5 years or older: 5 - 10 mg, repeated every 3 - 4 hours may be required to control tetanus spasms. Respiratory assistance should be available.

Status epilepticus and severe recurrent convulsive seizures. Infants over 30 days of age and children under 5 years: 0.2 - 0.5 mg slowly every 2 - 5 minutes up to a maximum of 5 mg (IV preferred). Children 5 years or older: 1 mg every 2 - 5 minutes up to a maximum of 10 mg (slow IV administration preferred). Repeat in 2 - 4 hours if necessary. EEG monitoring of the seizure may be helpful.

Compatibility. VALIUM should, as a matter of principle, be injected alone. In routine mixed injections, it is incompatible with aqueous solutions of other medicaments, and precipitation of the active substance will ensue. In 5 - 10% glucose infusion or in an equal volume of 0.9% saline, the active substance remains in solution sufficiently long without precipitation if handled as follows. The contents of the ampoules (not more than 4 mL) must be quickly and thoroughly mixed with the total volume of the infusion medium, which should be at least 250 mL, and infusion begun immediately.

OVERDOSAGE

Symptoms

Overdosage of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy. In more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory 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 overdose 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 contraindicated 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.

Contact the Poisons Information Centre for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

Ampoules

10 mg/2 mL: 5's
Store below 25 °C

Tablets

2 mg (white, scored, marked Roche 2 on reverse): 50's
5 mg (yellow, scored, marked Roche 5 on reverse): 50's
Store below 30 °C

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription only medicine

NAME AND ADDRESS OF THE SPONSOR

Roche Products Pty Limited
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