Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Ms Kate Doherty
Coroners Registrar
Coroners Court of Victoria
Level 11
222 Exhibition Street
MELBOURNE VIC 3000

Dear Ms Doherty

Subject: Investigation into the death of David A Trengrove

Thank you for your letter of 1 October 2012 to Ms Jane Halton PSM, Secretary to the Department of Health and Ageing ("the Department"), in relation to the above matter (your ref: COR 2008 004042). Ms Halton has referred the coroner's finding and recommendations to the Therapeutic Goods Administration (TGA) for consideration and response.

Specifically of relevance to the TGA, the coroner has recommended that *"to reduce the harms and death associated with benzodiazepine use in Victoria, within 12 months the Therapeutic Goods Administration of the Australian Government Department of Health and Ageing should move all benzodiazepines into Schedule 8 of the Standard for the Uniform Scheduling of Medicines and Poisons".*

Benzodiazepines are currently regulated in Australia as Schedule 4 ("prescription-only" medicines) ie. substances, the use or supply of which should be by or on the order of persons permitted by State or Territory legislation to prescribe and should be available from a pharmacist on prescription.

I have noted the coroner's findings that Mr Trengrove "died from the toxic effects of morphine in a setting of benzodiazepine dependency" and "from the unintentional consequences of his intentional use and abuse of prescription medication".

Morphine is currently regulated in Australia as a Schedule 8 ("controlled drug") ie. substances which should be available for use but require restriction of manufacture, supply, distribution, possession and use to reduce abuse, misuse and physical or psychological dependence.

Product Information / Consumer Medicine Information

As part of the TGA's regulatory processes for granting marketing authorization to prescription-only medicines in Australia, pharmaceutical companies must submit a "Product Information" document (PI) to the TGA for evaluation and approval. The PI provides health professionals with a summary of the scientific information relevant to the safe and effective use of a prescription or "pharmacist-only" (Schedule 3) medicine. It also provides objective information about the quality, safety and effectiveness of the medicine, as demonstrated in the data provided to the TGA by the company.

This information is intended to assist doctors, pharmacists and other health professionals in prescribing and dispensing medicines. In addition, this information can be used by health professionals in their consultations with patients, so that the patient can be better informed about their medicines.

The TGA's regulations also require that a Consumer Medicines Information (CMI) leaflet be made available to consumers either in the pack or in another manner that will enable the information to be given to the person to whom the medicines are administered or otherwise dispensed.

The CMI similarly contains information on the safe and effective use of medicines and are important because they provide information aimed at bringing about better health outcomes.

Since November 2009, improved access to prescription medicine information for consumers and health professionals has been achieved by facilitating access to a comprehensive source of up to date PI and CMI documents. What is provided, through the TGA website (http://www.tga.gov.au/about/ebs-picmi.htm), is a single trusted source of PI and CMI documents which support greater transparency of the regulatory process and is consistent with best international regulatory practice.

Analysis of a PI for a *diazepam* product

The coroner has found that Mr Trengrove was prescribed and dispensed diazepam 5mg x 50 tablets (amongst other medicines) at approximate weekly intervals from 6 March – 8 September 2008.

Consideration of the PI for "Valium" (one of the diazepam-based products marketed in Australia) (hardcopy attached), reveals that this medicine's Indications are –

- for the management of anxiety disorders or for the short term relief of the symptoms of anxiety. Anxiety of tensions 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; and
- as 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.

The PI also includes multiple Precautions about the use of this medicine. These include the advice that –

- in general, benzodiazepines should be prescribed for short periods (eg 2 – 4 weeks);
- continuous, long term use is not recommended;
- there is evidence that tolerance develops to the sedative effects;
- the medicine is not recommended as primary therapy in patients with depression and/or psychosis;
- the medicine may increase depression in some patients and may contribute to deterioration in severely disturbed schizophrenics with confusion and withdrawal;
- extreme caution must be exercised in administering the medicine 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;

- the use of benzodiazepines may lead to the development of physical and psychic dependence;
- the risk of dependence increases with dose and duration of treatment;
- dependence 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; and
- enhanced effects on sedation, respiratory depression and haemodynamic instability may occur when the medicine is co-administered with any centrally acting depressants, including narcotic analgesics.

Regulation of Schedule 8 medicines

In considering Schedule 8 medicines, there are significant, additional regulatory controls imposed upon these products (compared to other medicines) at the Commonwealth and State / Territory levels. These controls are in place in order to reduce abuse, misuse and physical or psychological dependence.

For example, the Department administers a legislatively-based control regime for illicit drugs covering border controls, manufacture and domestic transactions. The Department is responsible for granting permits and licenses that authorise the import and export of certain narcotic drugs, psychotropic substances, precursor chemicals, antibiotics and androgenic/anabolic substances controlled under the Customs (Prohibited Imports) Regulations and Customs (Prohibited Exports) Regulations.

The Department also collects data relating to domestic drug movements, manufacture and consumption from which it produces reports for State/Territory governments and to meet Australia's obligations to the United Nations International Narcotics Control Board.

TGA consideration of the coroner's recommendation

Turning to the coroner's "Findings, Comments and Recommendations", I have noted that "Associate Professor David Ranson and Dr Angela Sungaila were examined at length regarding the potential role that benzodiazepines – particularly diazepam – played in causing Mr Trengrove's death".

Although these expert witnesses testified that benzodiazepines might have contributed to Mr Trengrove's death, neither witness could definitively state that benzodiazepines had contributed to this outcome. A/Prof Ranson also testified that diazepam was noted in Mr Trengrove's initial toxicological analysis but at a level within therapeutic ranges.

I have also noted the coroner's "Concluding Comment" that –

> *The investigation into David's death has highlighted shortfalls in the prescribing practises of some doctors particularly with regard to benzodiazepines but it has also highlighted the absence of a reliable contemporaneous tool to support the prescribing needs and pressures of general practitioners per se. But doctors must also, as a matter of common practice, turn their mind to asking appropriate questions of their patients – questions about whether they attend other doctors, questions about other medication, questions about prior medical history. Any additional information disclosed by the patient can only serve the general practitioner well by enhancing their ability to treat and prescribe appropriately – and reduce harm.*

The coroner's recommendation to the Department follows Dr Sungaila's call "for a change to the scheduling from Schedule 4 to Schedule 8 because of the comparative addictive effects / potential for abuse of benzodiazepines to opioids".

Whilst Mr Trengrove's death was indeed a tragedy, when considering the information about the quality, safety and effectiveness of benzodiazepines and the entire circumstances of the case including those detailed above and –

- the finding that Mr Trengrove died from the toxic effects of morphine in a setting of benzodiazepine dependency;
- the uncertainty about the role that benzodiazepines played in Mr Trengrove's death;
- Mr Trengrove's medical history (including his "significant history of mental ill health including schizophrenia, depression and psychosis" and his "history of use of ecstasy, protein supplements, alcohol and injecting testosterone and other steroids");
- the multiple medications he was using at the time of his death;
- the prescribing and use of prescription-only benzodiazepines in a manner contrary to the medicine's published Product Information, including Mr Trengrove's abuse of these prescription medicines;
- Mr Trengrove's practice of "Doctor / Prescription Shopping";
- the admissions of Dr Thai Chin Lim "that his prescribing of benzodiazepines to Mr Trengrove was excessive and not correct";

in addition to factors such as -

- the lack of evidence that inclusion of benzodiazepines in Schedule 8 would have prevented Mr Trengrove's death, noting that general practitioners are still able to prescribe Schedule 8 medicines (albeit under a stricter regulatory framework);
- the further cost to Australian taxpayers of governments regulating benzodiazepines as Schedule 8 medicines;
- the additional regulatory impact upon the pharmaceutical industry of regulating benzodiazepines as Schedule 8 medicines; and
- that benzodiazepines continue to be supplied as prescription-only medicines in countries such as the United Kingdom and USA,

on balance, the TGA does not agree with the coroner's recommendation that all benzodiazepines should be moved into Schedule 8 of the Standard for the Uniform Scheduling of Medicines and Poisons.

Thank you again for raising this matter with the Department for its consideration.

Yours sincerely

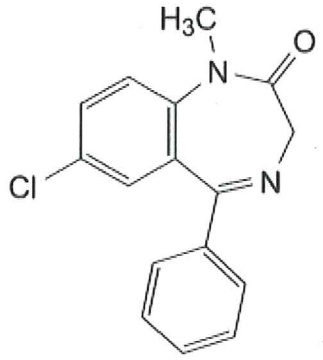
Dr John Skerritt
National Manager

6 November 2012

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.

Each 2 mg VALIUM tablet contains the following excipients: lactose, maize starch, magnesium stearate.

Each 5 mg VALIUM tablet contains the following excipients: lactose monohydrate, maize starch, iron oxide yellow CI77492, magnesium stearate.

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.

The oxidative metabolism of diazepam is mediated by CYP3A and CYP2C19 isoenzymes. Oxazepam and temazepam are further conjugated to with glucuronic acid.

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.

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. 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 PRECAUTIONS; Interactions with Other Medicines).

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.

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).

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.

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.

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.

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.

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).

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, 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.

Dependence

The use of benzodiazepines and benzodiazepine-like agents may lead to the development of physical and psychic dependence (see ADVERSE 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. 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

Enhanced effects on sedation, respiratory depression (including apnoea) and haemodynamic instability may occur when VALIUM is co-administered with any centrally acting depressants, 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.

Alcohol should be avoided in patients receiving VALIUM (see PRECAUTIONS).

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

The oxidative metabolism of diazepam, leading to the formation of nordiazepam and temazepam, is mediated predominantly by the CYP2C19 and CYP3A cytochrome P450 isoenzymes, respectively. Consequently, substrates which are modulators of CYP3A or CYP2C19, may potentially alter the pharmacokinetics of diazepam. Nordiazepam and temazepam are further metabolised to oxazepam.

Diazepam may interact with disulfiram, cimetidine, ketoconazole, fluvoxamine, fluoxetine, diltiazem or omeprazole resulting in increased plasma levels of VALIUM. Patients should be observed closely for evidence of enhanced benzodiazepine response (e.g. increased and prolonged sedation) 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.

See the OVERDOSAGE section for warnings about other central nervous system depressants, including alcohol.

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.

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.

Isolated instances of neutropenia have been seen.

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.

Nervous System Disorders: Amnesia, fatigue, drowsiness, muscle weakness, ataxia, dysarthria, slurred speech, headache, tremor, dizziness.

Psychiatric Disorders: Paradoxical reactions such as restlessness, acute hyperexcitation, agitation, irritability, anxiety, increased muscle spasticity, insomnia, sleep disturbances, nightmares, hallucinations, aggression, delusion, anger, psychoses, abnormal behaviour, stimulation and other adverse behavioural effects are known to occur when using benzodiazepines. Should these occur, use of the drug should be discontinued. They are more likely to occur in children and in the elderly.

Confusion, emotional poverty, alertness decreased, depression, libido increased or decreased.

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 (see PRECAUTIONS; Dependence).

Abuse of benzodiazepines has been reported (see PRECAUTIONS; Dependence)

Injury, Poisoning and Procedural Complications: An increased risk for falls and fractures has been reported in elderly benzodiazepine users.

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

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.

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, dysarthria, nystagmus, mental confusion and lethargy. In more serious cases, symptoms may include ataxia, areflexia, hypotonia, hypotension, apneoa, 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 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 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.

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

PRESENTATION AND STORAGE CONDITIONS

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

Disposal of Medicines

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 medicines should be returned to a pharmacy for disposal.

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription only medicine

NAME AND ADDRESS OF THE SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
4 - 10 Inman Road
Dee Why NSW 2099

Date of TGA Approval: 2 February 2010