AUSTRALIAN PRODUCT INFORMATION – NOUMED DIAZEPAM

(Diazepam)

1. NAME OF THE MEDICINE

Diazepam

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NOUMED DIAZEPAM tablets contain 5 mg of diazepam.

Contains excipients with known effects: lactose monohydrate.
For the full list of excipients, see Section ***6.1 List of excipients***.

3. PHARMACEUTICAL FORM

Noumed Diazepam Tablets containing 5 mg diazepam are white to off-white round flat bevelled edged uncoated tablets debossed with 5 and a scoreline on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Diazepam 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, diazepam may be useful in the symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis.

Diazepam 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

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
***Children – 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 to 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.

4.3 CONTRAINDICATIONS

Diazepam is contra-indicated in patients with:

- Known hypersensitivity to benzodiazepines
- Chronic obstructive pulmonary disease with incipient respiratory failure

Oral diazepam 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 diazepam. Such concomitant use has the potential to increase the clinical effects of diazepam, possibly including severe sedation, clinically relevant respiratory and/or cardiovascular depression (see *section 4.5 INTERACTIONS WITH OTHER MEDICINES*).

In general, benzodiazepines should be prescribed for short periods only (e.g. 2-4 weeks). Continuous long-term use of diazepam 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 benzodiapine).

Following the prolonged use of diazepam 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 four weeks to four months have been suggested. As with other benzodiazepines, when treatment is suddenly withdrawn, a temporary increase in sleep disturbance can occur after use of diazepam (see *section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Dependence*).

Since NOUMED DIAZEPAM 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, diazepam 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 behavior.

Acute Narrow-angle Glaucoma

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

Depression, Psychosis and Schizophrenia

Diazepam 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 behavior and other adverse behavioural effects, acute rage, stimulation or excitement may occur. Should such reactions occur, diazepam should be discontinued. They are more likely to occur in children and in the elderly.

Impaired Respiratory Function

Caution in the use of diazepam 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 diazepam 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 diazepam 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 *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. 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, diazepam 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 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.

Blood Dyscrasias

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.

Use in hepatic/renal impairment

Patients with impaired renal or hepatic function should use benzodiazepine medication with caution and dosage reduction may be advisable.

Use in the elderly

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

Efficacy and safety of diazepam 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. In view of lack of adequate clinical experience, chronic 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

Enhanced effects on sedation, respiratory depression (including apnoea) and haemodynamic instability may occur when diazepam 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 diazepam (see *section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE*).

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 diazepam. 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 anticholinergic effects of other drugs including atropine and similar drugs, antihistamines and antidepressants may be potentiated.

Interactions have been reported between some benzodiazepines and anticonvulsants, with changes in the serum concentration of the benzodiazepine or anticonvulsant. It is recommended that patients be observed for altered responses when benzodiazepines and anticonvulsants are prescribed together and that serum level monitoring of the anticonvulsant is performed more frequently.

See the *section 4.9 OVERDOSE* section for warnings about other central nervous system depressants, including alcohol.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Please see *section 5.3 PRECLINICAL SAFETY DATA: Impairment of fertility.*

Use in pregnancy

Category C

The safety of diazepam 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 diazepam 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).

Please see *section 5.3 PRECLINICAL SAFETY DATA: Teratogenicity.*

Use in lactation

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

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. As with all patients taking CNS depressant medications, patients receiving diazepam should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from diazepam therapy. Abilities may be impaired on the day following use.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

Isolated instance of neutropenia have been seen.

Dizziness has been reported occasionally with oral diazepam.

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 diazepam 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: Dependence*).

Abuse of benzodiazepines has been reported (see *section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE: Dependence*).

***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.

***Hepotabiliary Disorders**:* Very rarely jaundice.

***Haemopoietic Disorders**:* Isolated instances of neutropenia.

Reporting suspected adverse effects

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 *www.tga.gov.au/reporting-problems*.

4.9 OVERDOSE

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, disarthria, 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 may 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 with 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 seizures threshold (e.g. tricyclic antidepressants) and epileptic patients who have been treated with benzodiazepines. Refer to 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 Poison Information Centre on 131126 (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. This is presumed to be the result of facilitating the action in the brain of gamma-aminobutyric acid, a naturally occurring inhibitory transmitter.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Diazepam is rapidly and completely absorbed from the gastrointestinal tract, 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 mainly (about 70%) in the urine in free form or (predominantly) as conjugated metabolites. Diazepam and its metabolites cross the blood-brain and placental barriers and are also found in breast-milk.

Metabolism

Diazepam is metabolised to a hydroxyl-diazepam (temazepam) and nordiazepam ($t^{1/2}$ 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.

Excretion

The plasma concentration time curve of diazepam 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 to 48 hours). The elimination half-life is 90 hours at age 80 and increased two to three 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.

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 in mice and humans.

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. This was not observed in female rats and mice.

Impairment of Fertility

Reproductive studies in rats showed decreases in the number of pregnancies and in the number of surviving offspring following administration to both males and females prior to and during mating and throughout gestation and lactation.

Teratogenicity

Diazepam was found to be teratogenic in mice as well as in hamsters. Malformations included exencephaly, cranioschisis, kinking of the spinal cord, and cleft palate with and without cleft lip. Delayed development has been reported in offspring from several animal species treated with diazepam during pregnancy or during pregnancy and lactation.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The inactive ingredients are lactose monohydrate, maize starch, colloidal anhydrous silica,, magnesium stearate and purified talc.

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 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

PVC/PVdC/Al blister packs of 50 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

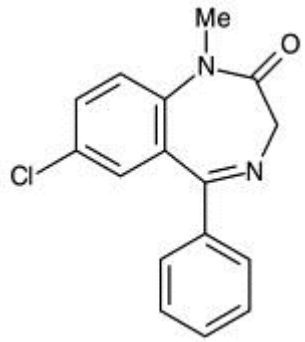
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Diazepam is a white or almost white crystalline powder, very slightly soluble in water, soluble in ethanol (96%).

Diazepam is a benzodiazepine derivative. Chemically, diazepam is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one.

Chemical structure:



Chemical name: 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

Molecular weight: 284.74

Molecular formula: $C_{16}H_{13}ClN_2O$

CAS number:

439-14-5

7. MEDICINE SCHEDULE (POISON STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

Avallon Pharmaceuticals Pty Ltd.Level 5, 7 Eden Park Drive
Macquarie Park NSW 2113

9. DATE OF FIRST APPROVAL

13 December 2019

10. DATE OF REVISION

06 February 2020

Summary table of changes

Section changed	Summary of new information
4.6	Minor editorial changes to refer to warnings inserted under Section 5.3
5.3	Updated warnings for genotoxicity, carcinogenicity, impairment of fertility and teratogenicity
6.1	Minor editorial changes to update name of the excipient
8	Update sponsor detail