AUSTRALIAN PRODUCT INFORMATION – DIAZEPAM ELIXIR (DIAZEPAM 10mg/10mL) ORAL LIQUID, SOLUTION

1 NAME OF THE MEDICINE

Diazepam

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient of Diazepam Elixir is diazepam 10mg/10mL.

Excipients with known effect: ethanol and sodium citrate dihydrate.

For the full list of excipients, see *Section 6.1 List of excipients*.

3 PHARMACEUTICAL FORM

Diazepam Elixir contains diazepam 10 mg per 10 mL. It is a clear, colourless to yellow, slightly viscous liquid with an odour of blackcurrant and is available in a 100mL amber glass bottle.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Diazepam is indicated in the management of anxiety disorders and for the short term relief of the symptoms of anxiety. Diazepam is a useful adjunct for the relief of reflex muscle spasm due to local trauma (injury, inflammation) to muscles, bones and joints. It is also indicated in the management of cerebral spasticity due to upper motor neuron lesions such as cerebral palsy and paraplegia, and spasticity in athetosis and stiff man syndrome. In acute alcohol withdrawal, diazepam may be useful in the symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis.

4.2 DOSE AND METHOD OF ADMINISTRATION

General

The lowest dose which can control the symptoms should be used. The dosage should be carefully individualised for maximum benefit. Dosage may need to be reduced in patients with hepatic or renal disease as the elimination half-life may be prolonged in this group. Treatment with benzodiazepines should always be withdrawn gradually. Elderly patients should be given a reduced dose. These patients should be checked regularly at the start of treatment in order to minimize the dosage and/or frequency of administration to prevent overdose due to accumulation.

In general benzodiazepines should be prescribed for short periods (for example 2-4 weeks). Long term use of diazepam is not recommended. There is evidence that tolerance develops to the sedative effects of benzodiazepines. Withdrawal symptoms can occur after one week's treatment, (e.g. rebound insomnia, following cessation of benzodiazepines).

Usual adult dose:	5 to 40mg (5 to 40mL) daily.
Average dosage for ambulatory patients:	2mg (2mL) three times daily or 5mg (5mL) in the evening and 2mg (2mL) once or twice during the day.
Elderly or debilitated patients:	2mg (2mL) twice daily or half the usual adult dose.
Children:	Benzodiazepines should not be given to children without careful assessment of the indication; duration of treatment must be kept to a minimum.
Children younger than 6 months of age:	Use not recommended.
6 months to 3 years:	1 to 6mg (1 to 6mL) daily.
4 to 14 years:	4 to 12mg (4 to 12mL) daily or calculated from 0.1 to 0.3mg/kg (0.1 to 0.3mL/kg) body weight.

Hospital treatment of tension, excitation, motor unrest:
10 to15 mg (10 to15mL) three times daily until the acute symptoms subside.

4.3 CONTRAINDICATIONS

Diazepam Elixir is contraindicated in patients with:

- Known hypersensitivity to benzodiazepines or to the excipients of the products (see *Section 6.1- List of Excipients*)
- Chronic obstructive airway disease with incipient respiratory failure
- Severe respiratory insufficiency
- Severe hepatic insufficiency
- Sleep apnoea syndrome
- Myasthenia gravis
- Alcohol dependence unless being treated for acute alcohol withdrawal

Diazepam should not be used as sole therapy for the treatment of depression or anxiety associated with depression as suicide may occur in such patients, nor should it be used as primary treatment of psychotic illness.

Diazepam Elixir is not recommended to control status epilepticus or other acute management situations.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use with Caution in the following circumstances

Hypotension: Diazepam should be administered with caution to patients in whom a drop in blood pressure might lead to cardiac or cerebral complications, although hypotension has occurred rarely. 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 can occur using therapeutic doses and the risk increases with higher doses. Amnesic 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).

Alcohol tolerance: Patients should be further advised that their tolerance for alcohol will be diminished and alcohol should therefore be avoided during treatment.

Prolonged use: Benzodiazepines should be prescribed for short periods only (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 cessation of recommended doses (e.g. rebound insomnia following cessation of a hypnotic benzodiazepine).

Withdrawal: Following prolonged use of diazepam withdrawal from medication should be gradual. A withdrawal timetable should be planned for each patient. For patients with known or suspected dependence withdrawal periods from four weeks to four months have been suggested.

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 behaviour and other reactions such as acute rage, stimulation or excitement may occur. If such reactions occur, diazepam should be discontinued. These reactions are more likely to occur in children and 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. Due to the risk of respiratory depression, lower doses are recommended for patients with chronic respiratory insufficiency.

Epilepsy: When diazepam is administered to patients with convulsive disorders an increase in the frequency and/or the 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.

Abuse: Caution must be exercised in administering diazepam to individuals known to be addiction prone or those with a history which 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 a withdrawal syndrome on discontinuation of the drug. The risk of dependence increases with dosage and the duration of treatment. Patients on long term therapy and/or high dosage can have more marked dependence and it occurs in predisposed patients with a history of drug and/or alcohol 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 particularly in those with drug seeking behaviour.

Withdrawal symptoms similar 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, delusional 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 the occurrence of withdrawal symptoms. Patients should be advised to consult their physician before 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 the symptoms beyond pretreatment levels following the cessation of the benzodiazepines. Rebound phenomena in general possibly reflect re-emergence of pre-existing symptoms combined with withdrawal symptoms described earlier. Withdrawal/rebound symptoms may follow high doses for relatively short periods.

Use in Hepatic and Renal Impairment

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 in liver enzymes, periodic blood counts and liver function tests are recommended.

Use in the Elderly

Such patients may be particularly susceptible to the sedative effects of benzodiazepines and associated giddiness, ataxia and confusion, which may increase the possibility 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 an inability to biotransform diazepam to inactive metabolites and so they, especially the very young, are usually more sensitive to it. Chronic use of diazepam is not recommended in children younger than 6 months due to a lack of adequate clinical experience.

Effects on laboratory tests

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

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

No effects on diagnostic tests have been seen when diazepam has been administered orally or rectally.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Diazepam produces additive CNS depressant effects when co-administered with other medications which themselves produce CNS depression, e.g. alcohol, barbiturates, anxiolytics, sedatives, antidepressants including tricyclic antidepressants, non selective MAO inhibitors, hypnotics, antiepileptic drugs, phenothiazines and other antipsychotics, skeletal muscle relaxants, antihistamines, narcotic analgesics and anaesthetics. The effect of these drugs may potentiate or be potentiated by diazepam.

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

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

Cisapride may lead to a temporary increase in the sedative effects of orally administered diazepam due to a faster absorption.

There is a potentially relevant interaction between diazepam and drugs that inhibit certain hepatic enzymes, particularly CYP3A4 and CYP2C19 which are the principal isoenzymes involved in the initial oxidative metabolism of diazepam. Potential hepatic enzyme inhibitors (eg cimetidine, omeprazole, disulfiram, fluvoxamine, fluoxetine, probenecid, ketoconazole, macrolide antibiotics such as erythromycin and clarithromycin, HIV-protease inhibitors such as ritonavir and indinavir, oral contraceptives) could decrease the rate of diazepam elimination and may lead to increased and prolonged sedation. Patients receiving diazepam should be monitored for signs of an exaggerated response if any of the above drugs are used concomitantly; some patients may require a reduction in diazepam dosage.

Inducers of hepatic enzymes (e.g. rifampicin, carbamazepine, phenytoin, and phenobarbitone) can increase the rate of elimination of diazepam.

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

There have been reports that the metabolic elimination of phenytoin is affected by diazepam.

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/m^2/day, twice the MRHD).

Use in pregnancy – Pregnancy Category C

The categorisation definition of Category C: Drugs which owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible.

The safety of diazepam for use in human pregnancy has not been established. An increased risk of congenital malformation associated with benzodiazepine use in the first trimester 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 new born infant. Continuous treatment during pregnancy and high doses in connection with delivery should be avoided.

Special care must be taken during labour and delivery; if diazepam is used as single high doses it may produce irregularities in the foetal heart rate, hypotonia, poor sucking, hypothermia, and moderate respiratory depression in the neonate. With newborn infants it must be remembered that the enzyme system involved in the breakdown of the drug is not yet fully developed, especially in premature infants. Withdrawal symptoms in new born infants have been reported with this class of drugs.

Use in lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Diazepam Elixir may modify patients' performance at skilled tasks (driving, operating machinery etc) to a varying degree depending upon dosage and individual susceptibility. Patients should be warned not to operate machinery or motor vehicles until it is known that they do not become drowsy or dizzy. Abilities may be impaired on the day following use.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Common (usually dose related)
Central Nervous System: fatigue, drowsiness, and ataxia
Musculoskeletal: muscle weakness

Uncommon
Cardiovascular: hypotension
Central Nervous System: amnesia (anterograde), confusion, depression, headache, tremor, vertigo, blurred vision, slurred speech and dysarthria
Dermatological: skin rash
Gastrointestinal: constipation, gastrointestinal disturbances, dry mouth, nausea and hypersalivation
Genito-urinary: incontinence, urinary retention, increase or decrease in libido

Rare
Central Nervous System: dizziness with oral diazepam
Cardiovascular: cardiac arrest

Very rare
Haematopoietic: isolated instances of neutropaenia have been reported
Hepatic: jaundice, elevated transaminases and alkaline phosphatase

Other
Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher doses. 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 diazepam should be discontinued.

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

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, mental confusion and lethargy. In more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, coma, and very rarely death.

Treatment: In the management of overdosage with any medication, it should be borne in mind that multiple agents may have been taken. Treatment should be symptomatic and supportive.

Following overdosage, activated charcoal should be administered within one to two hours after ingestion to decrease absorption. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube once the airway is protected. In the management of overdosage special attention should be paid to the respiratory and cardiovascular functions in intensive care. Hypotension and respiratory depression should be managed according to general principles.

Haemoperfusion and haemodialysis are not useful in benzodiazepine intoxication.

The benzodiazepine antagonist, flumazenil may be useful in hospitalised patients for the reversal of acute benzodiazepine overdose effects. The flumazenil product information should be consulted prior to use. The use of flumazenil is not recommended in epileptic patients who have been treated with diazepam. The reversal of the benzodiazepine effect in these patients may induce convulsions.

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 long acting benzodiazepine. Benzodiazepines, in general act as depressants of the central nervous system (CNS) and exhibit anxiolytic, anticonvulsant, sedative and muscle relaxant properties. Its actions are presumed to be mediated by enhancement of the activity of gamma-aminobutyric acid (GABA), the major natural inhibitory neurotransmitter in the brain. GABA acts at this receptor to open the chloride channel, allowing the flow of chloride ions into the neuron. Entry of chloride ions results in hyperpolarisation, which inhibits firing of the neuron and translates into decreased neuronal excitability, thus attenuating the effects of subsequent depolarising excitatory transmitters. Diazepam enhances the actions of GABA by causing GABA to bind more tightly to GABA type A receptors.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration diazepam is well absorbed from the gastrointestinal tract with peak plasma levels occurring within about 30 to 90 minutes.

Distribution

Diazepam is highly lipid soluble and widely distributed into body tissues and crosses the blood brain barrier. Diazepam and its metabolites also cross the placental barrier and are also distributed into breast milk. Diazepam is 98% protein bound in the plasma. The plasma concentration time curve is biphasic, with 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).

Metabolism

Diazepam is extensively metabolised to one major active metabolite (desmethyldiazepam), and two minor active metabolites, 3-hydroxydiazepam (temazepam) and 3-hydroxy-N-diazepam (oxazepam) in plasma. At therapeutic doses, desmethyldiazepam is found in plasma at concentrations equivalent to those of diazepam while oxazepam and temazepam are not usually detectable. Diazepam undergoes hepatic demethylation and hydroxylation, involving cytochrome P450 (CYP) 2C19 and CYP3A4 isoenzymes, followed by glucuronidation.

Excretion

It is largely excreted in the urine (70%), predominately as its conjugated metabolites or in its free form.

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).

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Ethanol, propylene glycol, glycerol, citric acid, sodium citrate dihydrate, purified water and blackcurrant flavour.

6.2 INCOMPATIBILITIES

Refer to *Section 4.5 - Interactions with Other Medicines and Other Forms of Interactions*.

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. Protect from light.
After opening store below 25°C and discard after 90 days.

6.5 NATURE AND CONTENTS OF CONTAINER

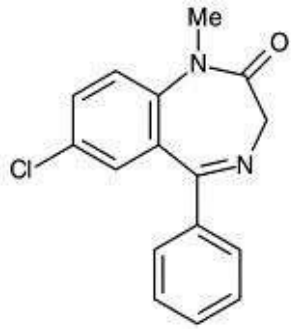
Diazepam Elixir is available in a 100mL amber glass bottle.

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

Chemical structure



Chemical Name: 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one.
Molecular Formula: $C_{16}H_{13}ClN_2O$
Molecular weight: 284.74
Diazepam is a benzodiazepine derivative. It is a colourless, crystalline compound, insoluble in water and soluble in alcohol.

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

30th September 2003

10 DATE OF REVISION

19th May 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
N/A	PI reformatted to align with new format
2 & 6.1	Correction of excipients to AAN

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