

AUSTRALIAN PRODUCT INFORMATION – DBL™ DIAZEPAM (Diazepam) INJECTION

1. NAME OF THE MEDICINE

Diazepam

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 mL ampoule contains diazepam 10 mg and the following inactive ingredients: propylene glycol 53% v/v, ethanol 31% v/v, in Water for Injections; pH 6.2 to 7.0.

Excipient(s) with known effect

Ethanol

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

3. PHARMACEUTICAL FORM

Benzodiazepine derivative is a colourless crystalline compound, insoluble in water. DBL Diazepam Injection is a clear colourless to pale yellow solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Management of anxiety disorders or for the short term relief of 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 spasms 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 diazepam is useful in controlling status epilepticus and the spasms of tetanus. Diazepam is also used as pre-operative medication.

4.2 Dose and Method of Administration

Dosage

Adults

The usual adult dose is 2 to 10 mg by intramuscular or intravenous injection repeated every three to four hours as required. In general, the maximum adult dose should not exceed 30 mg over an eight hour period.

Intravenous injections should be given into a large vessel, such as an antecubital vein, and the solution should be administered slowly at a rate not exceeding 5 mg/minute (see Section 4.4 Special warnings and precautions for use).

Cardioversion: To provide light anaesthesia and anterograde amnesia prior to cardioversion, 5 to 15 mg diazepam may be given by intravenous injection within 5 to 10 minutes before the procedure.

Endoscopic procedures: To reduce anxiety, diazepam may be administered by slow intravenous injection immediately before the procedure; dosage should be titrated to obtain the desired sedative response. Generally, a dosage of up to 10 mg is adequate, but up to 20 mg intravenously may be given, particularly if opiates are not given concomitantly. If the intravenous route is not feasible, 5 to 10 mg may be given intramuscularly approximately 30 minutes before the procedure.

Anticonvulsant: In the convulsing patient, it is preferred that diazepam be given intravenously. However, intramuscular injection may be used if intravenous administration is impossible. Initially, 5 to 10 mg may be given, repeated if necessary at 10 to 15 minute intervals up to a maximum dose of 30 mg. If necessary, a further dose may be repeated in 2 to 4 hours, however, residual active metabolites may persist and readministration should be made with this consideration.

Children

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

Intravenous administration should be made slowly over a 3 minute period at a dosage not exceeding 0.25 mg/kg. After an interval of 15 to 30 minutes, the initial dose may be repeated.

Status epilepticus and severe recurrent convulsive seizures: Slow intravenous administration is preferred.

Infants over 30 days of age and children under 5 years - 0.2 to 0.5 mg slowly every 2 to 5 minutes up to a maximum of 5 mg.

Children 5 years or older - 1 mg every 2 to 5 minutes up to a maximum of 10 mg. Repeat in 2 to 4 hours if necessary. EEG monitoring of the seizure may be helpful.

Tetanus: Infants over 30 days of age and children under 5 years - 1 to 2 mg intramuscularly or by slow intravenous injection, repeated every 3 to 4 hours as necessary.

Children 5 years and older - 5 to 10 mg repeated every 3 to 4 hours as necessary.

Method of Administration

Diazepam may be administered intravenously or intramuscularly (deep into the muscle). However, absorption following intramuscular administration is slow and erratic; thus this route of administration should be avoided if possible. Too rapid injection or the use of veins with too small a lumen carries the risk of syncope, apnoea, hypotension, bradycardia or cardiac or respiratory arrest 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 and extravasation must be strictly avoided because venous thrombosis, phlebitis, local

irritation, swelling, or less frequently, vascular changes may occur, particularly after rapid intravenous injection.

Lower doses should be used in the elderly, those with impaired hepatic or renal 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.

Use in one patient on one occasion only and discard any residue.

Compatibility

In general, the administration of diazepam by dilution or mixture with intravenous fluids or other drugs should be avoided. Diazepam may precipitate out of intravenous solutions and adsorbs to the plastic of intravenous bags and tubing. Where the administration of diazepam by intravenous infusion is indicated, Glucose Intravenous Infusion 5% or Sodium Chloride Intravenous Infusion 0.9% of minimum volume 250 mL should be used. The amount of diazepam added should not exceed 20 mg. The required dose of diazepam should be quickly and thoroughly mixed with the total volume of the infusion medium and the infusion begun immediately. The possibility of overloading the patient with fluid should be kept in mind.

4.3 Contraindications

Diazepam is contraindicated:

In patients with a known hypersensitivity to benzodiazepines or any of the excipients in DBL Diazepam injection.

In patients with severe respiratory failure, or chronic obstructive airways disease with incipient respiratory failure.

As sole therapy in psychosis including primary depressive disorders.

In patients with Myasthenia gravis.

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.

The drug should not be administered intravenously to patients in shock, coma, patients with cardiac or respiratory insufficiency or those with acute alcoholic intoxication with depressed vital signs.

4.4 Special Warnings and Precautions for Use

Concomitant use of alcohol/ central nervous system (CNS) depressants

Abilities may be impaired on the day following use. Patients should be advised that their tolerance for alcohol and other CNS depressants will be diminished. Concomitant use of diazepam with alcohol and/or with drugs, including opioids that have a depressive effect on the CNS should be avoided. These agents can enhance the clinical effects of diazepam and can possibly result in deep sedation, clinically significant respiratory and/or cardiovascular

depression, coma, and death. These medications should either be eliminated or limit dosages and durations to the minimum required in the presence of diazepam.

Tolerance

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

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

Circulatory consequences

Although hypotension has occurred only rarely, parenteral 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.

Memory impairment

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

Disorientation

Patients should be warned as to the possibility of prolonged disorientation due to the long half life of diazepam. This may especially be true where diazepam is used for premedication.

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

DBL Diazepam Injection is not recommended as primary therapy in patients with depression 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, DBL Diazepam Injection should be discontinued. They are more likely to occur in children and the elderly.

Epilepsy

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

Medical history of drug / alcohol abuse

Abuse of benzodiazepines has been reported. Extreme caution must be exercised in administering diazepam to individuals with a history of alcohol or drug abuse, dependence on CNS depressants or those known to be addiction prone or those whose history suggests they may increase the dosage on their own initiative.

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.

Prolonged use of diazepam may cause a diminished response to the effects of benzodiazepines.

Withdrawal

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 diazepam treatment is suddenly withdrawn, a temporary increase in sleep disturbance can occur (see Section 4.4 Special warnings and precautions for use, Dependence).

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 can range from headache, diarrhoea, muscle pain, insomnia, extreme anxiety, tension, restlessness, confusion and irritability, dysphoria, palpitations, panic attacks, vertigo, myoclonus, akinesia, hypersensitivity to light, sound and touch, abnormal body sensations (e.g. feelings 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 an extended period of time. However withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines administered continuously at therapeutic levels. Accordingly, DBL Diazepam Injection should be terminated by tapering the dose to minimise occurrence of withdrawal symptoms.

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. Withdrawal/rebound symptoms may follow high doses for relatively short periods.

Rebound anxiety

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

Injection technique

As a general rule, parenteral administration should only be done in a clinical setting (except in emergency cases) and measures for circulatory or respiratory life support should always be available.

When used intravenously, the following procedures should be adopted to reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling and rarely, vascular impairment: the solution should be injected slowly, taking at least one minute for each 5 mg (1 mL) given, into a large lumen vessel, such as an antecubital vein; do not use small veins such as those on the dorsum of the hand or wrist; extreme care should be taken to avoid intra-arterial administration or extravasation. Excessively rapid injection or administration into a small vein increases the risk of thrombophlebitis. Intra-arterial injection should be strictly avoided due to the danger of necrosis (see section 4.2 Dose and method of administration).

Careful monitoring is recommended after intravenous administration of diazepam. Upon discharge, the patient should be accompanied by another individual and should be warned not to drive a vehicle after drug administration. See section 4.7 Effects on Ability to Drive and Use Machines.

Intramuscular injection of diazepam can lead to a rise in serum creatinine phosphokinase activity, a maximum occurring twelve to twenty four hours after injection. (see section 4.8 Adverse Effects (Undesirable Effects) – Haematological). This fact should be taken into account in the differential diagnosis of myocardial infarction. In certain cases, IM route of administration should only be used if IV administration is not possible (refer to section 4.2 Dose and method of administration).

General

Dose of diazepam should be established individually based on the variable tolerance criteria of patients, particularly for those with physiological cerebral disorders (especially arteriosclerosis) or with cardiopulmonary insufficiency.

Impaired respiratory function

Caution in the use of parenteral 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. Diazepam should be used with caution in patients with sleep apnoea.

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 elevations of liver enzymes. Benzodiazepines may have a contributory role in precipitating episodes of hepatic encephalopathy in severe hepatic impairment.

As with other benzodiazepines, periodic blood counts and liver and kidney function tests are recommended, especially in the case of extended treatment.

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. Extreme care must be used in administering injectable diazepam, particularly by the intravenous 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 CNS depressants increases depression, with increased risks of apnoea. Lower doses should be used for elderly and debilitated patients.

Paediatric use

Efficacy and safety of parenteral diazepam have not been established in the neonate (30 days or less in age). Prolonged CNS depression has been observed in neonates due to inability to transform the drug.

Effects on laboratory tests

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

4.5 Interactions with Other Medicines and Other Forms of Interactions

Pharmacodynamic Drug-Drug Interaction

The benzodiazepines, including diazepam, produce additive CNS depressant effects when co-administered with other medications which themselves produce CNS depression, e.g. barbiturates, opioids, alcohol, anxiolytics, sedatives, antidepressants including tricyclic antidepressants and non-selective MAO inhibitors, hypnotics, antiepileptic drugs, phenothiazines and other antipsychotics, skeletal muscle relaxants, antihistamines, narcotic analgesics and anaesthetics (see Section 4.4 Special warnings and precautions for use). Therefore, it should be borne in mind that the effect of these drugs may potentiate or be potentiated by the action of DBL Diazepam Injection. Enhanced side effects such as sedation and cardio-respiratory depression may also occur when diazepam is co-administered with any centrally acting depressants including alcohol. 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.

See section 4.9 Overdose for warning of other central nervous system depressants including alcohol.

There are several reports of severe hypotension, cardiorespiratory depression, excessive sedation or loss of consciousness in patients receiving combined treatment with clozapine and

benzodiazepines, including diazepam. Concomitant use of diazepam and clozapine is not recommended.

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

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

When combined with methadone diazepam may enhance euphoria, leading to an increased risk of abuse or dependence. Diazepam increased the subjective and sedative opioid effects of methadone in a manner that may heighten abuse potential. A significantly greater deterioration in reaction time was observed compared to methadone alone.

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

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

Diazepam pretreatment changes the pharmacodynamics and pharmacokinetics of the anaesthetic ketamine. Ketamine N-demethylation was inhibited leading to a prolonged half-life and prolonged ketamine-induced sleeping time. In the presence of diazepam, a reduced ketamine concentration is required to achieve adequate anaesthesia.

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

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

Pharmacokinetic drug-drug-interactions

There is a potentially relevant interaction between diazepam and compounds which inhibit certain hepatic enzymes (particularly cytochrome P450 III A). Data indicate that these compounds influence the pharmacokinetics of diazepam and may lead to increased and prolonged sedation.

Diazepam undergoes oxidative metabolism, and consequently may interact with disulfiram, cimetidine, ketoconazole, fluvoxamine, fluoxetine or omeprazole, diltiazem, idelalisib, clarithromycin, erythromycin, ritonavir and verapamil resulting in increased plasma levels of diazepam. Patients should be observed closely for evidence of enhanced benzodiazepine response during concomitant treatment with these drugs; some patients may require a reduction in benzodiazepine dosages.

The metabolism of diazepam and its main metabolite, desmethyldiazepam depends on the cytochrome P450 isozymes CYP3A4 and CYP2C19. Modulators of these enzymes may lead to changes in diazepam disposition and effects. Stronger interactions are seen with compounds that affect more than one of diazepam's oxidative metabolic pathways. Inhibitors of CYP3A4 and CYP2C19 decrease metabolic rate and may lead to higher than normal concentrations of diazepam and the desmethyl metabolite and consequently to increased/ prolonged sedation and anxiolytic effects. Such changes may exacerbate diazepam's effects in patients with increased sensitivity, e.g. due to their age, reduced liver function or treatment with other drugs that impair oxidation. Inducers of CYP3A4 and CYP2C19 may lead to lower than expected concentrations and hence to a lack of desired efficacy.

Effect of other drugs on the pharmacokinetics of diazepam

Enzyme inhibitors

Grapefruit juice contains strong inhibitors of CYP3A4. Diazepam exposure was strongly increased (AUC 3.2-fold; C_{max} 1.5-fold) and time to reach maximum concentration was delayed when diazepam was given with grapefruit juice instead of water. This may result in excessive or prolonged sedation. Patients should be advised to avoid grapefruit juice while administering diazepam.

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

The serotonin reuptake inhibitor fluvoxamine also inhibits both of diazepam's CYP3A4 and CYP2C19 degradation pathways. In a clinical trial using a single dose of 10 mg diazepam, fluvoxamine increased not only the AUC of diazepam 3-fold and prolonged its elimination half-life from 51 h to 118 h, but also increased exposure and time to reach steady state of the desmethyl metabolite. Fluoxetine is a moderate inhibitor of CYP3A4. Fluoxetine showed a more moderate effect on diazepam AUC (approximately 50% increase) and did not affect psychomotor response because combined concentrations of diazepam and desmethyldiazepam were similar with and without fluoxetine. Fluvoxamine and fluoxetine may lead to increased and prolonged sedation. For patients taking fluvoxamine, a benzodiazepine metabolised via a non-oxidative pathway is recommended. Patients receiving fluoxetine with diazepam should be monitored closely.

Combined hormonal contraceptives appear to reduce the clearance (by 40%) and prolong elimination half-life (by 47%) of diazepam. Diazepam-induced psychomotor impairment in women on contraceptives may be higher during the 7-day menstrual pause when off the hormone preparation than when taking the contraceptive. Monitor the clinical response to diazepam in women taking concomitant oral contraception. There is some limited evidence

that benzodiazepines can increase the incidence of break-through bleeding in women with hormonal contraceptives.

The proton pump inhibitor omeprazole, a CYP2C19 and CYP3A4 inhibitor, administered at a dose of 20 mg daily increased the diazepam AUC by 40% and the half-life by 36%; at a dose of 40 mg daily, omeprazole increased the diazepam AUC by 122% and the half-life by 130%. The elimination of desmethyldiazepam was reduced as well. The effect of omeprazole was seen in extensive but not slow metabolisers of CYP2C19. Esomeprazole (but not lansoprazole or pantoprazole) has the potential to inhibit the metabolism of diazepam to a similar degree as omeprazole. Patients administering these drugs with diazepam should be monitored closely and the dose of diazepam should be reduced if necessary.

The histamine H₂-receptor antagonist cimetidine, an inhibitor of multiple CYP isozymes, including CYP3A4 and CYP2C19, reduces the clearance of diazepam and of desmethyldiazepam by 40 to 50%. This results in higher exposure to and a prolonged elimination half-life of diazepam and its main metabolite after single dosing and to higher steady-state concentrations after multiple dosing of diazepam. Enhanced sedation was seen with co-administration of cimetidine. Therefore, when used with cimetidine, a reduction in the dose of diazepam may be necessary. Ranitidine and famotidine do not affect the hepatic elimination of diazepam.

Disulfiram inhibits the metabolism of diazepam (median decrease in clearance 41%, increase in half-life 37%) and probably the further metabolism of diazepam's active metabolites. Enhanced sedative effects may result.

Antituberculosis therapy may change the disposition of diazepam. In the presence of isoniazid diazepam mean exposure (AUC) and half-life were increased (on average 33-35%) with the largest changes seen in subjects with slow-acetylator phenotype. When used with isoniazid, monitor patients and reduce the dose of diazepam if necessary.

The calcium channel blocker diltiazem, a substrate for the same CYP isozymes as diazepam and an inhibitor of CYP3A4, increased AUC (by approximately 25%) and prolonged half-life (by 43% in extensive CYP2C19 metabolisers) of diazepam with little differences between subjects with different CYP2C19 phenotypes. In the presence of diltiazem exposure to desmethyldiazepam also tended to increase. Exercise caution when using diazepam with diltiazem, irrespective of CYP2C19 metaboliser status.

The primary metabolite of idelalisib is a strong CYP3A4 inhibitor and increases the serum concentrations of diazepam so that dose reduction may have to be considered.

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

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

Enzyme inducers

Rifampicin potently induces CYP3A4 and also has a significant accelerating effect on the CYP2C19 pathway. When dosed at 600 mg daily for 7 days, diazepam clearance was increased 4.3-fold and AUC decreased by 77%. A significant reduction in exposure to all diazepam metabolites was also observed. Doubling the daily rifampicin dose did not further increase its effect. Diazepam should only be used together with rifampicin if no therapeutic alternative exists.

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

Effect of diazepam on the pharmacokinetics of other drugs

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

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

Diazepam may decrease the control of Parkinsonian symptoms in patients taking levodopa. Diazepam should therefore be administered with caution to patients who are taking levodopa.

4.6 Fertility, Pregnancy and Lactation

Effects on fertility

Reproductive studies in rats showed decreases in the number of pregnancies and in the number of surviving offspring following administration of oral doses of 100 mg/kg/day (22-fold the MRHD on a body surface area basis) to both males and females prior to and during mating and throughout gestation and lactation. No adverse effects were observed at 10 mg/kg/day (60 mg/m²/day, twice the MRHD).

Use in pregnancy –Category C

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

The safety of diazepam for use in human pregnancy has not been established. Diazepam and its metabolites readily cross the placenta. Do not administer diazepam during the first trimester of pregnancy. 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, respiratory depression and hypothermia in the newborn infant. Continuous treatment during pregnancy and administration of high doses in connection with delivery should be avoided. Infants born of mothers taking benzodiazepines chronically during the later stages of pregnancy may develop physical dependence. 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 suckling, 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).

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.

Published animal studies of some anaesthetic/analgesic/sedation drugs that are N-methyl-D-aspartate (NMDA) antagonists or GABAergic agonists have reported adverse effects on brain development in early life and late pregnancy (see Section 5.3 Preclinical Safety Data).

Use in lactation

Diazepam is excreted in human breast milk, and may cause drowsiness and feeding difficulties in the infant. Since diazepam passes into breast milk, injectable diazepam should not be administered to breastfeeding mothers, or breastfeeding should be suspended if the product is to be given regularly.

4.7 Effects on Ability to Drive and Use Machines

Sedation, amnesia, impaired concentration and impaired muscle function may adversely affect the ability to drive or operate machinery. Prior to receiving diazepam, patients should be warned not to operate dangerous machinery or drive motor vehicles until completely recovered. The physician should decide when these activities may be resumed.

If sleep duration is insufficient or alcohol and/or other CNS depressant drugs are consumed, the likelihood of impaired alertness may be increased (see section 4.5 Interactions with other medicines and other forms of interactions).

4.8 Adverse Effects (Undesirable Effects)

More common reactions

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

Less common reactions

The following effects are encountered infrequently:

Haematological

Blood dyscrasias including neutropenia, agranulocytosis, anaemia, leukopenia, thrombocytopenia. Intramuscular injection (but not intravenous injection) may lead to a rise in serum creatinine phosphokinase activity, a maximum occurring twelve to twenty four hours after injection. This fact should be taken into account in the differential diagnosis of myocardial infarction.

Cardiac disorders

Hypotension, Bradycardia, cardiac failure including cardiac arrest, tachycardia, palpitations, ventricular premature contractions and other arrhythmias.

The propylene glycol in DBL Diazepam Injection may lead to cardiovascular depression.

Vascular disorders

Hypotension, circulatory depression.

Eye disorders

Conjunctivitis, blurred vision, diplopia.

Ear and labyrinth disorders

Vertigo.

Respiratory, thoracic and mediastinal disorders

Decreased gag reflex. Coughing, dyspnoea, respiratory depression including respiratory failure, hyperventilation, laryngospasm, and pain in the throat or chest.

The propylene glycol in DBL Diazepam Injection may lead to respiratory depression.

Renal and urinary disorders

Urinary retention, difficulty in micturition, incontinence.

Gastrointestinal disorders

Nausea and vomiting, diarrhoea, constipation, gastrointestinal disorders, dry mouth or hypersalivation.

Skin and subcutaneous tissue disorders

Skin reaction, rash, urticaria, pruritus, photosensitivity.

Musculoskeletal and connective tissue disorders

Muscular weakness, muscle cramps.

Hepatobiliary disorders

Hepatic dysfunction, jaundice.

Nervous system disorders

Amnesia, confusion, headache, slurred speech, consciousness decreased, lightheadedness, syncope, dysarthria, aphasia, tremor, nystagmus.

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

Diazepam may produce increased incidence and severity of seizures, especially on withdrawal of diazepam in patients with epilepsy or a history of seizures.

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

Psychiatric disorders

Agitation, depression, libido disorder, flat affect, numbed emotion, irritability, confusional state, emotional and mood disturbances.

Paradoxical reactions such as restlessness, delusion, psychosis, anxiety, acute hyperexcitation, acute disorientation, nervousness, hostility, anger, panic, aggression, auditory and visual hallucinations, increased muscle spasticity, insomnia, rage, nightmares, abnormal dreams, sleep disturbances, stimulation, hyperactivity, inappropriate behaviour and other adverse behavioural effects have been reported; should these occur, use of diazepam should be discontinued. They are more likely to occur in children and in the elderly.

Emergence or worsening of mental depression, including suicidal ideation, also has been associated with benzodiazepine use, principally in patients with pre-existing depression.

Chronic use (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena (see section 4.4 Special warnings and precautions for use).

Abuse of benzodiazepines has been reported (see section 4.4 Special warnings and precautions for use).

Immune system disorders

Immediate hypersensitivity reactions.

General disorders and administration site conditions

Body and joint pains, hyperpyrexia, hypothermia, fatigue.

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.

Injection site reactions

Injection site reactions such as venous thrombosis, phlebitis, pain, local irritation and swelling, or less frequently, vascular changes, may occur (particularly after rapid intravenous injection). Intramuscular administration can result in local pain, in some cases accompanied by erythema, at the site of injection. Tenderness is relatively common.

Investigations

Heart rate irregular, blood alkaline phosphatase increased, blood creatine phosphokinase increased, transaminases increased (see also above – Haematological).

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, dysarthria, nystagmus, mental confusion and lethargy. In more serious cases, symptoms may include ataxia, areflexia, apnoea, hypotonia, hypotension, cardiorespiratory depression, coma, and very rarely death. Coma may be more protracted and cyclical, particularly in elderly patients.

The respiratory depression effects associated with benzodiazepines are more serious in patients with respiratory disorders.

Benzodiazepines increase the effects of alcohol and other drugs with a depressive activity on the CNS. When combined with other CNS depressants, the effects of overdosage are likely to be severe and may prove fatal.

Treatment

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

Treatment is purely supportive of respiratory and cardiovascular function, vital signs should be monitored and supportive measures should be applied according to the clinical status of the patient. Special attention should be paid to these functions in intensive care. Maintenance of adequate pulmonary ventilation is essential. The use of pressor agents intravenously may be necessary to combat hypotension. Fluids should be administered intravenously to encourage diuresis. Haemoperfusion and haemodialysis are not useful in benzodiazepine intoxication.

The benzodiazepine antagonist flumazenil may be used in hospitalised patients for the reversal of acute benzodiazepine effects. Please consult the flumazenil product information prior to usage. This drug should be administered only under strictly 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 must be used with extreme caution in the presence of drugs which can lower the convulsive threshold (e.g. tricyclic antidepressants). The use of flumazenil is not recommended in epileptic patients who have been treated with diazepam (or any other benzodiazepine). The reversal of the benzodiazepine effect could induce convulsions in such patients.

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

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 (GABA), a naturally occurring inhibitory neurotransmitter.

The effects of diazepam may result from action in the limbic and subcortical levels of the CNS. Benzodiazepines are capable of producing all levels of CNS depression (i.e. mild sedation to hypnosis to coma).

Clinical trials

No data available

5.2 Pharmacokinetic Properties

Absorption

Diazepam may be given by intravenous (IV) or intramuscular (IM) injection, but absorption following intramuscular administration may be slow and erratic, depending on the muscle mass used and other factors. When diazepam is injected into the deltoid muscle, absorption is usually rapid and complete.

Distribution

Plasma concentrations of diazepam and its active metabolites exhibit considerable interpatient variation, and therapeutic plasma concentrations are difficult to define. Diazepam is 98% protein bound in the plasma. Diazepam and its metabolites readily diffuse across the blood-brain barrier and placenta. They also appear in the milk of breastfeeding mothers.

During repeated dosing of diazepam, accumulation of diazepam and its active metabolites may occur. Accumulation continues until a steady state plasma concentration is reached, which usually takes 5 days to 2 weeks after initiation of therapy.

Metabolism

The plasma concentration time curve is biphasic; an initial rapid and extensive distribution phase with a half life of up to three 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.

The drug is metabolised in the liver to hydroxy-diazepam (temazepam) and nordiazepam ($t_{1/2}$ approximately 96 hours) and ultimately to oxazepam.

The elimination of diazepam after reaching steady state levels is slow since active metabolites may remain in the blood for several days or even weeks, possibly resulting in persistent effects. The elimination half life may be prolonged in the newborn infant, 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.

Excretion

Diazepam is excreted mainly (about 70%) in the urine in free form or predominantly as glucuronide and sulphate metabolites.

5.3 Preclinical Safety Data

Effect of anaesthetic and sedative drugs on brain development in early life and late pregnancy

Published studies in pregnant and juvenile animals demonstrate that the use of anaesthetic/analgesic and sedation drugs that block NMDA receptors and/or potentiate GABA

activity during the period of rapid brain growth or synaptogenesis may result in neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis when exposed for longer than 3 hours. These studies included anaesthetic agents from a variety of drug classes. The clinical significance of these nonclinical findings is yet to be determined.

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/m²/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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Ethanol

Propylene glycol

Sodium hydroxide

Water for injections

6.2 Incompatibilities

See Section 4.2 Dose and Method of Administration, Compatibilities.

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.

6.5 Nature and Contents of Container

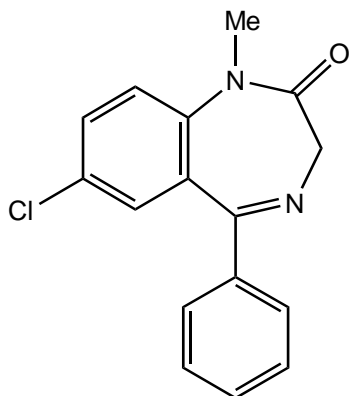
DBL Diazepam Injection 10 mg/2 mL is available in packs of 5 and 50 ampoules.

6.6 Special Precautions for Disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical Properties

Chemical structure



Benzodiazepine derivative. Chemical name: 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. MW: 284.74.

CAS number

439-14-5

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedinfo.com.au

9. DATE OF FIRST APPROVAL

16 February 2005

10. DATE OF REVISION

29 September 2022

Summary Table of Changes

Section changed	Summary of new information
Throughout	Minor editorial changes
4.4	Additional safety information in the subsection Medical History of Drug / Alcohol Abuse.

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