NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DBL™ DIAZEPAM 10mg/2mLSolution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2mL ampoule contains diazepam 10 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
clear colourless solution, pH 6.2 – 7.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tension and anxiety states; status epilepticus; as preoperative medication; skeletal muscle spasm and motor unrest, cerebral palsy, athetosis, stiff-man syndrome, tetanus, acute agitation due to alcohol withdrawal.

4.2 Dose and method of administration

Diazepam may be administered intravenously or intramuscularly (deep into the muscle). However, absorption following I.M. administration is slow and erratic; thus this route of administration should be avoided if possible.

Adults:
The usual adult dose is 2-10 mg I.M. or I.V. repeated every 3-4 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 - PRECAUTIONS 13).

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

Endoscopic Procedures: To reduce anxiety, diazepam may be administered slowly I.V. 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 I.V. may be given, particularly if opiates are not given concomitantly. If the I.V. route is not feasible, 5-10 mg may be given I.M. approximately 30 minutes before the procedure.

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

Children:

I.V. administration should be made slowly over a 3 minute period in a dosage not exceeding 0.25 mg/kg. After an interval of 15-30 minutes, the initial dose may be repeated.
Status Epilepticus and Severe Recurrent Convulsive Seizures:
Slow I.V. administration is preferred.
Infants over 30 days of age and children under 5 years: 0.2-0.5 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: 1-2 mg I.M. or I.V. slowly, repeated every 3 to 4 hours as necessary.
Children 5 years and older: 5-10 mg repeated every 3 to 4 hours as necessary.

4.3 Contraindications
Diazepam is contraindicated:

1. In patients with a known hypersensitivity to benzodiazepines.
2. In patients with chronic obstructive airways disease with incipient respiratory failure.
3. As sole therapy in psychosis including primary depressive disorders.
4. 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.

4.4 Special warnings and precautions for use

1. 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.
2. 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 of sleep disturbance can occur (see PRECAUTIONS, Dependence).
3. 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 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).

Risks from Concomitant Use with Opioids:
Concomitant use of benzodiazepines, including diazepam, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of benzodiazepines and opioids for use in patients for whom alternative treatment options are inadequate.
Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe diazepam concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when diazepam is used with opioids (see section 4.5).

PRECAUTIONS

1. 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.
2. 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.

3. 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.

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

5. 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. As with other benzodiazepines, periodic blood counts and liver-function tests are recommended.

6. Depression, Psychosis and Schizophrenia:
DBL™ Diazepam Injection is not recommended as primary therapy in patients with depression or psychosis (see section 4.3). 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.

7. 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.

8. Elderly or Debilitated Patients:
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.

9. 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.

10. 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.
11. Abuse: Extreme caution must be exercised in administering diazepam to individuals with a history of alcohol or drug abuse or those known to be addiction prone or those whose history suggests they may increase the dosage on their own initiative.

12. Dependence:  
The use of benzodiazepines may lead to dependence as defined by the presence of a withdrawal syndrome on discontinuation of the drug. The risk of dependence increases with dose and duration of treatment. It is more pronounced in patients on long term therapy and/or high dosage and particularly so in predisposed patients with a history of alcohol or drug abuse. Tolerance as defined by a need to increase the dose in order to achieve the same therapeutic effect seldom occurs in patients receiving recommended doses under medical supervision. Tolerance to sedation may occur with benzodiazepines, especially in those with drug seeking behaviour.

Withdrawal symptoms similar in character to those noted with barbiturates and alcohol have occurred once physical dependence to benzodiazepines has developed or following abrupt discontinuation of benzodiazepines. These symptoms can range from insomnia, anxiety, 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.

13. Injection Technique:  
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.

USE IN CHILDREN  
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.

4.5 Interaction with other medicines and other forms of interaction  
1. The benzodiazepines, including diazepam, produce additive CNS depressant effects when co-administered with other medications which themselves produce CNS depression, e.g. barbiturates, 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-WARNINGS). 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.

2. The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at GABA_A sites, and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepine and opioids and follow patients closely for respiratory depression and sedation.
3. Concomitant use with alcohol is not recommended due to enhancement of the sedative effect.

4. 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.

5. Diazepam undergoes oxidative metabolism, and consequently may interact with disulfiram, cimetidine, ketoconazole, fluvoxamine, fluoxetine or omeprazole 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.

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

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

8. 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 be performed more frequently.

9. Isoniazid may increase plasma diazepam levels.

10. Rifampicin may enhance the elimination of diazepam, leading to decreased plasma diazepam levels.

11. 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.

**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.

### 4.6 Fertility, pregnancy and lactation

**Pregnancy**

Category C

The safety of diazepam for use in human pregnancy has not been established. 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. 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 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).

**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.

### 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 DBL™ Diazepam Injection should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from parenteral diazepam. 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 and that these medications should either be eliminated or given in reduced dosage in the presence of diazepam.

4.8 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 neutropaenia, agranulocytosis, anaemia, leukopaenia, thrombocytopaenia. 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.

Cardiovascular
Hypotension, bradycardia and cardiac arrest, tachycardia, palpitations. Ventricular premature contractions and other arrhythmias.
The propylene glycol in DBL™ Diazepam Injection may lead to cardiovascular depression.

Ophthalmic
Conjunctivitis, nystagmus, blurred vision, diplopia.

Respiratory system
Decreased gag reflex. Coughing, dyspnoea, respiratory depression, hyperventilation, laryngospasm, and pain in the throat or chest.
The propylene glycol in DBL™ Diazepam Injection may lead to respiratory depression.

Genitourinary
Urinary retention, difficulty in micturition, incontinence.

Gastrointestinal
Nausea and vomiting, diarrhoea, constipation, gastrointestinal disturbance, dryness of mouth or hypersalivation.

Hepatobiliary
Elevated transaminases and alkaline phosphatase, hepatic dysfunction, jaundice.

Neurological (CNS)
Vertigo, amnesia, confusion, mental depression, headache, slurred speech, numbed emotion, reduced alertness, lightheadedness, syncope.
Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher doses. Amnestic effects may be associated with inappropriate behaviour. Paradoxical reactions such as anxiety, acute hyperexcitation, panic, aggression, auditory and visual hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of diazepam should be discontinued. Emergence or worsening of mental depression, including suicidal ideation, also has been associated with benzodiazepine use, principally in patients with pre-existing depression. 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.

Hypersensitivity and dermatological
Rash, urticaria, pruritus, photosensitivity, immediate hypersensitivity reactions.

Body as a whole
Increase or decrease in libido, tremor, body and joint pains, muscle cramps, muscular weakness, hyperpyrexia, hypothermia.

**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.

**Reporting of Suspected Adverse Reactions**
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

### 4.9 Overdose

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 is purely supportive of respiratory and cardiovascular function, and 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. 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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

### 5. PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Diazepam appears to act at the limbic and subcortical levels of the central nervous system producing anxiolytic, sedative, skeletal muscle relaxant and anticonvulsant effects.

#### 5.2 Pharmacokinetic properties

Diazepam may be given by I.V. or I.M. injection but absorption following I.M. administration is slow and erratic. The drug is metabolised in the liver and the metabolites are excreted mainly as glucuronides in the urine and faeces. Diazepam readily diffuses across the placenta and appears in the milk of nursing mothers.

#### 5.3 Preclinical safety data

Not applicable.

### 6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients

Propylene glycol 53% v/v
Ethanol absolute 31% v/v in Water for Injections

6.2 Incompatibilities

In general, diazepam should not be mixed or diluted with other drugs nor should it be added to I.V. fluids, the exception being either Glucose Intravenous Infusion 5% or Sodium Chloride Intravenous Infusion 0.9% of volumes greater than 250 mL. The amount of diazepam added should not exceed 20 mg. The possibility of overloading the patient with fluid should be kept in mind.

6.3 Shelf life

36 months from date of manufacture stored at or below 25°C

6.4 Special precautions for storage

Protect from light.

6.5 Nature and contents of container

2mL of solution for injection in a glass ampoule in pack sizes of 5 or 50.

6.6 Special precautions for disposal and other handling

If only part used, discard the remaining solution.
No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7. MEDICINE SCHEDULE

Controlled Drug (C5)

8. SPONSOR

Pfizer New Zealand Limited,
PO Box 3998
Auckland, New Zealand, 1140

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

17/5/1979

10. DATE OF REVISION OF THE TEXT

01 September 2017

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<td>4.5</td>
<td>Addition of the text regarding concomitant use of opioids, benzodiazepines and other central nervous system depressants.</td>
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