AUSTRALIAN PRODUCT INFORMATION – DBL™ DIAZOXIDE INJECTION BP (Diazoxide)

1. NAME OF THE MEDICINE

Diazoxide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL Diazoxide Injection BP is a sterile solution of Diazoxide BP in Water for Injections BP. Each 20 mL ampoule contains 300 mg of diazoxide.

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

3. PHARMACEUTICAL FORM

DBL Diazoxide Injection BP is a clear colourless solution for intravenous injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Diazoxide is a non-diuretic antihypertensive agent. It is administered by rapid IV injection for emergency reduction of blood pressure in patients with malignant hypertension when prompt and urgent decrease in diastolic pressure is required. DBL Diazoxide Injection BP is recommended in the treatment of hypertensive crises associated with acute glomerular nephritis, acute hypertensive encephalopathy, cerebral haemorrhage or congestive heart failure.

Diazoxide is usually effective in patients with refractory hypertension not responsive to other agents. It has also been used in the treatment of chronic hypertension to control elevated blood pressure before commencement of therapy with oral antihypertensive agents.

In order to reduce the danger of haemorrhage due to elevated blood pressure, DBL Diazoxide Injection BP may be used in hypertensive patients undergoing diagnostic procedures such as renal biopsy or arteriography.

4.2 Dose and Method of Administration

Dosage

The usual adult dose of diazoxide for the treatment of hypertension is 300 mg administered undiluted by rapid intravenous (IV) injection over a period of 30 seconds or less. Children and unusually large or small adults may be given 5 mg/kg bodyweight. Recent studies have shown that minibolus IV administration of diazoxide in doses of **1 to 3mg/kg** every 5 to 15 minutes may be as effective as the administration of a single 300 mg intravenous dose and may be associated with fewer adverse effects.

Method of Administration

Following intravenous administration of diazoxide, blood pressure should be closely monitored until it has stabilised, and hourly thereafter. Further reduction in blood pressure 30 minutes or more after injection should be investigated for causes other than the effects of the drug. The patient should remain recumbent for at least 30 minutes after injection. In ambulatory patients, final blood pressure measurements should be made while the patient is standing.

Repeated administration of DBL Diazoxide Injection BP at 4 to 24 hourly intervals is generally sufficient to maintain blood pressure below pretreatment levels. Administration of DBL Diazoxide Injection BP for more than 5 days is seldom necessary and oral antihypertensive agents should replace diazoxide therapy as soon as adequate blood pressure control has been achieved.

4.3 Contraindications

Diazoxide is contraindicated in patients who are hypersensitive to it or other thiazide derivatives. Diazoxide is not recommended for use in hypertension due to mechanical abnormality, eg aortic coarctation or arteriovenous shunt.

4.4 Special Warnings and Precautions for Use

DBL Diazoxide Injection BP is for intravenous administration only. Due to the high alkalinity of the injection, it should not be administered intramuscularly, subcutaneously, or into body cavities. Care should be taken to avoid extravascular injection or leakage.

Patients receiving diazoxide should be carefully observed for possible development of severe hyperglycaemia. This is especially important in patients with renal insufficiency or impaired carbohydrate metabolism. During intravenous therapy with diazoxide, blood glucose levels should be monitored daily.

Diazoxide should be administered with caution in patients in whom retention of sodium and water or abrupt reductions in blood pressure may be hazardous, eg those with impaired cardiac or cerebral circulation.

Caution should be exercised when administering diazoxide to uremic patients as they may experience a greater hypotensive effect. Haematological monitoring for signs of leucopenia and thrombocytopenia may be advisable in patients on prolonged diazoxide therapy.

Serum uric acid should be monitored in patients with hyperuricaemia or a history of gout.

Use in the elderly

No data available

Paediatric use

In children, it is recommended that bone and psychological maturation and growth should be regularly assessed.

Reports of pulmonary hypertension in neonates and infants treated for hyperinsulinaemic hypoglycaemia

There have been post-marketing reports of pulmonary hypertension occurring in infants and neonates treated with diazoxide for hyperinsulinaemic hypoglycaemia. The cases were reversible upon discontinuation of the drug. Patients under treatment, especially those with risk factors for pulmonary hypertension, should be monitored for respiratory distress. Diazoxide should be discontinued if pulmonary hypertension is suspected.

Note - DBL Diazoxide Injection BP is not indicated for the treatment of hyperinsulinaemic hypoglycaemia.

Reports of necrotising enterocolitis (NEC) in neonates and infants

There have been post-marketing reports of necrotising enterocolitis, including fatal cases, occurring in infants and neonates treated for off-label indications with diazoxide. Closely monitor patients for signs and symptoms of necrotising enterocolitis, especially those with increased risk factors (such as pre-term infants and use of higher doses of diazoxide). Discontinue diazoxide if NEC is suspected.

Effects on laboratory tests

No data available

4.5 Interactions with Other Medicines and Other Forms of Interactions

Concomitant administration of diuretics may result in potentiation of the hyperglycaemic, hyperuricaemic or hypotensive effect of diazoxide. Diazoxide may potentiate the hypotensive effect of other antihypertensive agents; this effect is usually used to therapeutic advantage, but careful adjustment of dosage is necessary when these drugs are used concomitantly.

4.6 Fertility, Pregnancy and Lactation

Effects on fertility

No data available

Use in pregnancy – Category C

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

Safe use of diazoxide in pregnancy has not been established. It is a powerful relaxant of uterine smooth muscle and may arrest labour. Uterine contractions can, however, be re-established with oxytocic agents. Diazoxide crosses the placenta and although hypertensive crises of eclampsia have been treated fairly successfully with diazoxide, the possibility of adverse effects on the foetus cannot be excluded. Hyperglycaemia has been observed in the newborn.

Use in lactation

No data available

4.7 Effects on Ability to Drive and Use Machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse Effects (Undesirable Effects)

Although numerous adverse effects may occur in patients receiving prolonged diazoxide therapy, serious adverse effects rarely occur when the drug is administered intravenously for short periods of time.

Hyperglycaemia frequently occurs in patients on intravenous diazoxide therapy. Although this is usually mild and subsides without treatment, administration of oral hypoglycaemic agents or insulin may be required, especially in diabetic patients or those receiving repeated doses of diazoxide. Hyperglycaemic effects of diazoxide are potentiated in the presence of hypokalaemia.

Sodium and water retention occur frequently and may result in oedema, weight gain, congestive heart failure and refractoriness to the hypotensive effects of the drug. However, these may be prevented by appropriate diuretic therapy.

Severe hypotension occurs infrequently and can be treated if necessary with sympathomimetic agents such as noradrenaline.

Other adverse effects resulting from the vasodilatory action of intravenous diazoxide include flushing, generalised or localised sensations of warmth, burning or itching, headache, sweating, lightheadedness and transient weakness.

Transient myocardial or cerebral ischaemia may occur. When diazoxide is administered intravenously, pain or a feeling of warmth frequently occurs along the injected vein.

Gastrointestinal upsets including nausea, vomiting and abdominal discomfort are frequent, but usually transient.

Hypersensitivity reactions such as rash, leucopenia, fever and thrombocytopenia occur infrequently.

Pulmonary hypertension has been reported in neonates and young infants treated with diazoxide for hyperinsulinaemic hypoglycaemia. (see section 4.4 Special Warnings and Precautions for Use).

There have been post-marketing reports of pericardial effusion with diazoxide use for hyperinsulinaemic hypoglycaemia, mostly in paediatric patients and infants.

Note – DBL Diazoxide Injection BP is not indicated for the treatment of hyperinsulinaemic hypoglycaemia.

Necrotising enterocolitis, including fatal cases, has been reported in neonates and young infants treated with diazoxide (see section 4.4 Special Warnings and Precautions for Use).

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

Overdosage of diazoxide produces hyperglycaemia and possibly ketoacidosis which should be treated promptly with insulin and restoration of fluid and electrolyte balance. Severe hypotension can be controlled with sympathomimetic agents if necessary. Diazoxide has a long half-life and therefore prolonged surveillance of overdose patients is recommended.

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

Diazoxide reduces peripheral vascular resistance and blood pressure through a direct vasodilatory effect on smooth muscle in peripheral arterioles. Although the precise mechanism of its hypotensive effect is not yet understood, it has been postulated that antagonism of calcium may be involved. Diazoxide-induced decreases in blood pressure are accompanied by reflex increases in heart rate and cardiac output.

Clinical trials

No data available

5.2 Pharmacokinetic Properties

Absorption

Following rapid intravenous administration diazoxide produces a prompt reduction in blood pressure; maximum hypotensive effects generally occur within less than 5 minutes. Blood pressure usually rises rapidly over the next 10 to 20 minutes, followed by a more gradual increase as pretreatment levels are approached. The duration of the antihypertensive effect of diazoxide varies greatly - generally 3 to 12 hours, but may be much longer in some cases. The hypotensive response may be greater and more prolonged with subsequent intravenous doses.

Distribution

Diazoxide crosses the placenta and blood-brain barrier. In plasma, approximately 90% of diazoxide is protein-bound. However, the extent of protein-binding may be reduced in uremic patients. The high degree of protein-binding is responsible for the prolonged half-life of diazoxide which averages approximately 28 hours in adults, but may be shorter in children or prolonged in patients with renal impairment.

Metabolism

Diazoxide is partly metabolised in the liver.

Excretion

Diazoxide is excreted in the urine both unchanged and in the form of metabolites. Only small amounts are recovered from the faeces.

5.3 Preclinical Safety Data

Genotoxicity

No data available

Carcinogenicity

No data available

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sodium hydroxide

Water for injections

6.2 Incompatibilities

Diazoxide has been found to be incompatible with hydralazine hydrochloride, lignocaine hydrochloride and propranolol hydrochloride. Do not dilute. Diazoxide is to be administered undiluted rapidly for maximum effect. Slower administration may reduce the antihypertensive response.

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. Avoid excessive heat and freezing.

6.5 Nature and Contents of Container

Code	Strength	Volume	Pack
2270A	300 mg	20 mL ampoule	1's

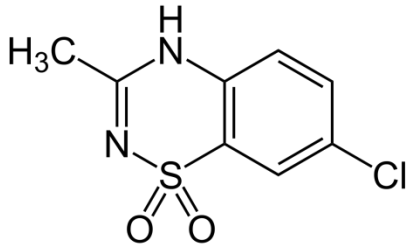
6.6 Special Precautions for Disposal

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

6.7 Physicochemical Properties

The pH of the solution is adjusted to approximately 11.5 with Sodium Hydroxide BP.

Chemical structure



CAS number

364-98-7

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.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

08 October 1991

10. DATE OF REVISION

1 May 2024

Summary Table of Changes

Section changed	Summary of new information
4.4	Addition of information regarding postmarketing reports of Necrotising Enterocoloitis
4.8	Addition of information regarding postmarketing reports of Necrotising Enterocoloitis