NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DBL™ Ephedrine Sulfate Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL™ Ephedrine Sulfate Injection is a sterile solution of Ephedrine Sulfate in Water for Injections. Each mL contains 30 mg of Ephedrine Sulfate and 3 mg of Sodium Chloride in Water for Injections.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

DBL™ Ephedrine Sulfate Injection is a sterile solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DBL™ Ephedrine Sulfate Injection is indicated in the treatment of shock unresponsive to fluid replacement. It is also indicated in the treatment of hypotension secondary to spinal anaesthesia. DBL™ Ephedrine Sulfate Injection has also been used in the treatment of bronchial asthma and reversible bronchospasm although more selective agents (beta-adrenergic agonists) are now available.

4.2 Dose and method of administration

DBL™ Ephedrine Sulfate Injection is administered by the intramuscular, subcutaneous or intravenous route. Patients in shock may require intravenous administration to ensure absorption of the drug. When administered intravenously, the injection should be given slowly. Care should be taken to avoid extravasation, since this may result in tissue necrosis and sloughing. Ephedrine sulfate should be administered in the lowest effective dose. The parenteral adult dose should not exceed 150 mg in 24 hours.

As a pressor:

Adult dose: The usual adult dose is 25-50 mg (range 10-50 mg) administered intramuscularly or subcutaneously. Additional doses should be based on patient response. The intravenous route may be used if an immediate response is required. The dosage for the intravenous route is 10-25 mg which may be repeated every 5-10 minute until the desired response is obtained.

Paediatric dose: The recommended paediatric dose is 3 mg/kg/day or 100 mg/m^2/day via the intravenous or subcutaneous route, given in 4-6 divided doses.

During therapy with a pressor agent, blood pressure should be elevated to slightly less than the patient's normal blood pressure. In previously normotensive patients, systolic blood pressure should be maintained at 80-100 mmHg. In previously hypertensive patients, systolic blood pressure should be maintained at 30-40 mmHg below their usual blood pressure. In some patients with very severe hypotension, maintenance of even lower blood pressure may be desirable if blood or fluid volume replacement has not been completed.

Bronchospasm:

Adult dose: The usual adult dose is 12.5-25 mg, given intramuscularly, subcutaneously or intravenously. Further dosage should be determined by patient's response.

Paediatric dose: The usual paediatric dose is 3 mg/kg or 100 mg/m^2 intravenously or subcutaneously, given in 4-6 divided doses.

Compatibilities

Ephedrine sulfate is reported to be compatible with 0.9% sodium chloride, lactated Ringer's injection, and 10% glucose in water.

4.3 Contraindications

DBL™ Ephedrine Sulfate Injection is contraindicated in closed angle glaucoma, since ephedrine may exacerbate the condition.

Ephedrine sulfate is contraindicated in patients with pheochromocytoma, since severe hypertension may result.

Ephedrine sulfate is contraindicated in patients with asymmetric septal hypertrophy (idiopathic hypertrophic subaortic stenosis) since the obstruction may increase as myocardial contractility improves.

Ephedrine sulfate is contraindicated in patients undergoing therapy with monoamine oxidase inhibitors (MAO inhibitors), or within 14 days of ceasing such therapy, since MAO inhibitors may prolong and intensify the cardiac and pressor effects of ephedrine.

Ephedrine sulfate is contraindicated in patients undergoing general anaesthesia with cyclopropane or halothane or other halogenated hydrocarbons, since anaesthesia may increase cardiac irritability which may lead to arrhythmias.

Ephedrine sulfate is contraindicated in patients with tachyarrhythmias or ventricular fibrillation, since exacerbation of these conditions may occur.

Ephedrine sulfate is also contraindicated in patients with hypersensitivity to ephedrine and in patients with psychoneurosis.

4.4 Special warnings and precautions for use

The use of ephedrine as a pressor agent is not a substitute for replacement of blood, plasma, fluids and/or electrolytes. Blood volume depletion should be corrected as fully as possible before ephedrine therapy is instituted. In an emergency, ephedrine may be used as an adjunct

to fluid volume replacement or as a temporary supportive measure to maintain coronary and cerebral artery perfusion until volume replacement therapy can be completed, but ephedrine must not be used as sole therapy in hypovolaemic patients.

Ephedrine may deplete noradrenaline stores in sympathetic nerve endings resulting in reduced cardiac and pressor effects of the drug. Consequently, it may be necessary to administer noradrenaline to replace tissue stores for restoration of the pressor effects of ephedrine.

Prolonged administration of pressor agents has been associated with oedema, haemorrhage, focal myocarditis, subpericardial haemorrhage, necrosis of the intestine and hepatic and renal necrosis. Since these effects have generally been observed in patients with severe shock and it is not clear if the drug or the shock state itself was responsible, they should therefore be taken into consideration before ephedrine sulfate is used.

Hypoxia, hypercapnia and acidosis may also reduce the effectiveness or increase the incidence of adverse effects of ephedrine, and should be identified and corrected prior to or concurrently with administration of the drug.

Ephedrine sulfate should be used with caution, if at all, in patients with hypertension or hyperthyroidism, since there is an increased risk of adverse effects in these patients.

Ephedrine sulfate should also be used with caution in geriatric males, especially those with prostatic hypertrophy, since ephedrine may cause acute urinary retention.

Ephedrine sulfate should also be used with caution in diabetic patients since drug induced hyperglycaemia may result in loss of diabetic control.

Ephedrine sulfate should also be used with caution in patients with cardiovascular disease including angina, cardiac arrhythmia and coronary insufficiency, since the cardiovascular effects of ephedrine may exacerbate these conditions. Ephedrine may intensify the ischaemia in myocardial infarction by increasing myocardial oxygen demands.

Patient Monitoring

Cardiovascular parameters, including blood pressure, ECG, cardiac output, central venous pressure and pulmonary artery pressure should be monitored during therapy with ephedrine. Urinary output should also be monitored.

4.5 Interaction with other medicines and other forms of interaction

α-blockers: α-blockers may decrease the vasopressor effect of ephedrine.

Atropine sulfate: Atropine sulfate may increase the vasopressor effect of ephedrine.

β-blockers: β-blockers may inhibit the cardiac and bronchodilator effects of ephedrine.

Cardiac glycosides: Concurrent use of cardiac glycosides and ephedrine may increase the risk of arrhythmias.

Ergotamine, ergometrine, methylergometrine, oxytocin: Concurrent use of these drugs with ephedrine sulfate may result in a potentiation of the pressor effect of ephedrine. Concurrent use of ergotamine and ephedrine sulfate may also produce peripheral vascular ischaemia and gangrene.

Guanethidine: Ephedrine sulfate may decrease the antihypertensive effect of guanethidine.

Hydrocarbon inhalation anaesthetics, such as cyclopropane, halothane: These drugs may increase cardiac irritability, and concurrent use with ephedrine sulfate may lead to increased risk of arrhythmia (see section 4.3).

Methyldopa: Concurrent use of methyldopa with ephedrine sulfate may result in a reduced pressor effect.

Monoamine Oxidase (MAO) Inhibitors: Concurrent use of MAO inhibitors and ephedrine sulfate may result in potentiation of the cardiac and pressor effects of ephedrine (see section 4.3).

Reserpine: Concurrent use of reserpine with ephedrine sulfate may result in a reduced pressor effect.

Sympathomimetic Agents: Concurrent use of ephedrine sulfate and other sympathomimetics may result in increased cardiovascular and pressor effects and an increased risk of adverse effects.

Tricyclic antidepressants: Concurrent use of tricyclic antidepressant and ephedrine may result in potentiation of the cardiovascular and pressor effects of ephedrine.

Clonidine: Pretreatment with clonidine may increase the pressor effect of ephedrine.

Urinary Alkalinizers, such as acetazolamide, dichlorphenamide, sodium bicarbonate and sodium citrate: These drugs may increase the half-life and decrease the elimination of ephedrine leading to enhanced therapeutic or toxic effects of ephedrine.

Theophylline: Concurrent use of ephedrine and theophylline may result in an increased incidence of adverse effects than when either drug is used alone. Adverse effects include those in the central nervous and the gastrointestinal systems

4.6 Fertility, pregnancy and lactation

Fertility

No data available.

Pregnancy

Category A: Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

DBL™ Ephedrine Sulfate Injection may accelerate the foetal heart rate when used to control maternal hypotension during spinal anaesthesia for delivery. DBL™ Ephedrine Sulfate Injection should not be used if the maternal blood pressure is greater than 130/80 Hg.

Lactation

Ephedrine sulfate is distributed into breast milk, and therefore DBL™ Ephedrine Sulfate Injection is not recommended for use during lactation because of the risk of adverse effects in the infant.

4.7 Effects on ability to drive and use machinery

No data available.

4.8 Undesirable effects

Body as a whole: pallor, fever, headache, dryness of nose, mouth and throat.

Ephedrine sulfate is reported to cause physical addiction after excessive long term use. Addiction is more likely to occur after oral use, since intramuscular, subcutaneous or intravenous administration of ephedrine sulfate would not normally occur over long periods.

Cardiovascular system: angina, palpitations, bradycardia, tachycardia, hypertension, hypotension, extrasystole and pericardial pain. Arrhythmias, including ventricular fibrillation, may occur, especially in patients with organic heart disease or those receiving other drugs that sensitise the heart to arrhythmias.

Digestive system: nausea, vomiting, mild epigastric distress.

Nervous system: nervousness, anxiety, restlessness, insomnia, mood or mental changes, fear, irritability, trembling. Large doses may cause dizziness, lightheadedness, vertigo, confusion, delirium, euphoria. Long-term therapy in large doses may lead to psychosis characterized by paranoia, hallucinations, depression and bizarre mentation.

Genito-urinary system: difficult or painful urination, acute urinary retention (especially with prostatic hypertrophy).

Respiratory system: shortness of breath, respiratory difficulty, dyspnoea.

Skin and appendages: sweating.

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

Symptoms associated with overdosage of ephedrine include headache, severe nausea or vomiting, chills or fever, dizziness or lightheadedness, anxiety, nervousness, restlessness, mood changes, convulsions, severe weakness, blurred vision or enlarged pupils, ongoing fast heartbeat, severe or ongoing chest pain, severe hypertension or hypotension, and severe breathing difficulties.

Paranoid psychosis, delusions and hallucinations may also follow ephedrine overdosage.

Treatment

Treatment of overdose involves the following measures:

- reduce dosage or discontinue administration of ephedrine
- general supportive therapy, including monitoring and maintaining vital signs, blood gases, electrolytes and ECG.

The following additional measures may need to be considered:

- β-blockers (eg. propranolol) to control tachycardia and arrhythmia
- phentolamine or nitroprusside to reduce severe hypertension
- diazepam to control convulsions. General anaesthesia and neuromuscular blocking agents may need to be considered to treat refractory seizures
- dexamethasone to treat pyrexia

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

The molecular formula of Ephedrine Sulfate is (C10H15NO)2H2SO4. Its molecular weight is 428.5. The CAS registry number of Ephedrine Sulfate is 134-72-5.

Mechanism of action

Ephedrine is a sympathomimetic which stimulates both alpha and beta adrenergic receptors, and also releases noradrenaline from storage site. The main effects of therapeutic doses of ephedrine are relaxation of bronchial smooth muscle, cardiac stimulation and increased systolic and usually diastolic blood pressure via an increase in cardiac output and peripheral vasoconstriction. Ephedrine also decreases intestinal tone and motility, relaxes the bladder wall, contracts the sphincter muscle, relaxes the detrusor muscle, and decreases uterine activity. Ephedrine also has central nervous system stimulant effects. Tachyphylaxis to the effects of ephedrine may also occur after use for a short while possibly due to the depletion of noradrenaline stores.

5.2 Pharmacokinetic properties

Ephedrine is rapidly absorbed after intramuscular or subcutaneous administration. The onset of action after intramuscular administration is 10-20 minutes, and the duration of pressor and cardiac responses to ephedrine is 1 hour after intravenous administration of 10-25 mg or intramuscular or subcutaneous administration of 25-50 mg. Small quantities of ephedrine are metabolised in the liver, but the majority of ephedrine is excreted unchanged in the urine. The plasma half life of ephedrine is 3-6 hours. Elimination of ephedrine is increased (and hence the half life is decreased) with decreasing pH of the urine. Ephedrine is presumed to cross the placenta, and to be excreted into breast milk.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

Reproductive and developmental toxicity

No data available.

6. PHARMACEUTICAL PARTICUALRS

6.1 List of excipients

- 3 mg of Sodium Chloride
- Water for Injections.

6.2 Incompatibilities

Ephedrine sulfate is reported to be physically incompatible with the phenobarbitone sodium, pentobarbitone sodium, quinalbarbitone sodium and thiopentone sodium, and with hydrocortisone sodium succinate in some infusion solutions.

6.3 Shelf life

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

6.4 Special precautions for storage

Store below 25°C, protect from light.

6.5 Nature and contents of container

Ephedrine sulfate 30 mg/mL 5 x 1 mL ampoules

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Class B2 Controlled Drug

8. SPONSOR

Pfizer New Zealand Limited

P O Box 3998

Auckland, New Zealand

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

8 March 1984

10. DATE OF REVISION OF THE TEXT

22 January 2019

Summary table of changes

Section changed	Summary of new information
All	Reformatting according to new Medsafe Datasheet guidance