NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DBL™ Adrenaline 1:1000 (1 mg/mL) and 1:10,000 (1 mg/10 mL) solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL Adrenaline 1:1000 (1 mg/mL) and 1:10,000 (1 mg/10 mL) solution for injection is a sterile, clear, colourless aqueous solution.

Each ampoule of DBL Adrenaline Injection 1:1,000 contains 1.8 mg of adrenaline acid tartrate (equivalent to 1 mg of adrenaline)/mL of water.

Each ampoule of DBL Adrenaline Injection 1:10,000 contains 1.8 mg of adrenaline acid tartrate (equivalent to 1 mg of adrenaline)/10 mL of water.

Excipient(s) with known effect

Each ampoule contains 1 mg/mL of sodium metabisulfite and 8 mg/mL of sodium chloride.

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

3. PHARMACEUTICAL FORM

Solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DBL Adrenaline 1:1,000

For the treatment of acute allergic reactions, life-threatening angioneurotic oedema and anaphylactic shock resulting from reactions to drugs, animal serums, insect stings and other allergens.

DBL Adrenaline 1:10,000

Adjunctive use in the management of cardiac arrest and anaphylactic shock resulting from reactions to drugs, animal serums, insect stings and other allergens.

4.2 Dose and method of administration

DBL Adrenaline injection does not contain any preservatives. It is for single use in one patient only. Discard any residue.

Do not use if the injection is brown or contains a precipitate.

Adrenaline is given by subcutaneous injection. It may also be administered intramuscularly but not into the buttocks.

In extreme emergencies, where a more rapid effect is required, adrenaline may be given by slow intravenous injection or by slow intravenous infusion but **only as a dilute solution (1 in 10,000 or 1 in 100,000).**

Acute allergic reactions, life-threatening angioneurotic oedema and anaphylactic shock

DBL Adrenaline 1:1,000 administered by intramuscular or subcutaneous injection

When used in anaphylactic shock, volume replacement is an essential concomitant treatment since effective intravascular volume may have been depleted by increased vascular permeability in anaphylaxis.

For the relief of anaphylactic shock and life threatening angioneurotic oedema, adrenaline should be administered by intramuscular injection.

For acute allergic reactions due to insect stings, etc., either the intramuscular or subcutaneous route may be used.

Adults

0.3 to 0.5 mL (0.3-0.5 mg) of DBL Adrenaline 1:1,000, administered slowly. The dose may be repeated every 10 minutes if necessary. In severe reactions the dose can be increased to 1 mL.

Paediatric population

0.1 to 0.5 mL (0.1-0.5 mg) of DBL Adrenaline 1:1,000 depending on age or 0.05 mL (50 micrograms (mcg) for infants under 1 year.

Cardiac resuscitation and aanaphylactic shock

DBL Adrenaline 1:10,000 only administered intravenously

Adults

In cardiopulmonary resuscitation the initial dose is 10 mL (1 mg of DBL Adrenaline 1:10,000) delivered intravenously, preferably through a central line, and repeated as often as every 2 to 3 minutes during CPR for up to an hour. Depending on the arrhythmia the dose may be increased after three injections of 1 mg to 5 mg or 0.1 mg/kg bodyweight.

Further bolus doses or continuous infusion may be required to maintain an adequate blood pressure after the patient generated pulse has returned.

Paediatric population

In cardiopulmonary resuscitation, the dose is 0.1 mL/kg bodyweight of DBL Adrenaline 1:10,000 (0.01 mg/kg) intravenously initially then 1 mL/kg bodyweight (0.1 mg/kg). Doses may be repeated every five minutes if necessary.

For anaphylactic shock, if intravenous administration is required the dose is 0.1 mL/kg bodyweight of DBL Adrenaline 1:10,000 (0.01 mg/kg) at a rate of 1 mL (0.1 mg) or less per minute.

4.3 Contraindications

Adrenaline is contraindicated in patients with known sensitivity to adrenaline or sympathomimetic amines and any ingredients listed in Section 6.1 List of excipients, hyperthyroidism, hypertension, ischaemic heart disease, diabetes mellitus or narrow angle glaucoma.

Adrenaline should not be used in the presence of cardiac dilation or coronary insufficiency.

Adrenaline should not be used in most patients with arrhythmias, cerebral arteriosclerosis and conditions where vasopressor drugs may be contraindicated, e.g., in thyrotoxicosis.

Adrenaline should not be used in obstetrics when maternal blood pressure is in excess of 130/80. During labour, adrenaline may delay the second stage by inhibiting spontaneous or oxytocin induced contractions of the pregnant human uterus. See also Sections 4.5 Interaction with other medicines and other forms of interaction and 4.6 Fertility, pregnancy and lactation).

Adrenaline is also contraindicated in shock (other than anaphylactic shock) in patients with phaeochromocytoma, organic brain damage.

Concurrent use of adrenaline with general anaesthesia, such as halogenated hydrocarbons, cyclopropane or similar volatile anaesthetics may produce fatal ventricular arrhythmias (see Section 4.5 Interaction with other medicines and other forms of interaction).

Adrenaline should not be injected into fingers, toes, ears, nose or genitalia. There is a danger of vasoconstriction producing sloughing of tissues in these areas.

4.4 Special warnings and precautions for use

Disease states

Use with extreme caution in patients with cardiovascular disease including ventricular fibrillation, prefibrillatory rhythm tachycardia, myocardial infarction, phenothiamine induced circulatory collapse, cerebrovascular insufficiency, angina pectoris and prostatic hypertrophy or psychoneurosis.

Use with extreme caution in patients with chronic lung disease, long-standing bronchial asthma and emphysema who have developed degenerative heart disease. Anginal pain may be induced when coronary insufficiency is present.

Syncope has occurred following administration to asthmatic children.

In patients with Parkinsonian Syndrome, the drug increases rigidity and tremor.

Diabetic patients

A greater increase may be produced in heart rate, blood glucose, lactate, glycerol and free fatty acids when adrenaline is administered to diabetic patients with autonomic neuropathy than in diabetic patients without neuropathy (see Contraindication).

Circulatory support

When adrenaline is used for circulatory support, correction of hypovolaemia, metabolic acidosis, and hypoxia or hypercapnia should be carried out beforehand or concomitantly.

Sodium metabisulfite

DBL Adrenaline contains a sulfate which may cause allergic type reactions in certain susceptible individuals. The possibility of an allergic reaction to sodium metabisulfite should be considered in asthmatic patients who show paradoxical worsening of their condition following use of the drug.

Other beta-agonist sympathomimetics

Allow sufficient time to elapse before or after administering another beta-agonist sympathomimetic agent to avoid additive effects (see Section 4.5 Interaction with other medicines and other forms of interaction).

Gangrene

Intra-arterial administration should be avoided since marked vasoconstriction may result in gangrene. Local ischaemic necrosis can occur from repeated injections in one site.

Intramuscular injection into the buttocks should be avoided as gas gangrene is a possibility.

Use in renal impairment

Parenterally administered adrenaline initially may produce constriction of renal blood vessels and decrease urine formation and large doses may cause complete renal shutdown.

Use in elderly patients

The adult dose is used but should be given very slowly with caution as these patients may be more sensitive to adrenaline. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

4.5 Interaction with other medicines and other forms of interaction

Sympathomimetic agents

Adrenaline should not be administered concomitantly with other sympathomimetic agents because of the possibility of additive effects and increased toxicity.

Rapidly acting vasodilators

Rapidly acting vasodilators can counteract the marked pressor effects of adrenaline.

General anaesthetics

Administration of halothane or other similar volatile anaesthetics such as cyclopropane and trichlorethylene that increase cardiac irritability and seem to sensitise the myocardium to adrenaline may result in arrhythmias including ventricular premature contractions, tachycardia or fibrillation and acute pulmonary oedema if hypoxia is present.

Cardiovascular drugs

Adrenaline should not be used in patients receiving high dosage of other drugs, e.g., quinidine, digoxin and other cardiac glycosides, that can sensitise the heart to arrhythmias. The risk of cardiac arrhythmias is higher when adrenaline is given to patients receiving digoxin or quinidine and other cardiac glycosides.

Antihypertensive therapy

Special care is advisable in patients receiving antihypertensive therapy as severe hypertension may result. Adrenaline may antagonise the neuron blockade produced of antihypertensives, such as guanethidine resulting in decreased antihypertensive effect.

Alpha adrenergic blocking agents

Alpha-blockers antagonise the vasoconstriction and hypertension effects of adrenaline. Adrenaline specifically reverses the antihypertensive effects of adrenergic neurone blockers with the risk of severe hypertension.

Beta adrenergic blocking agents

Severe hypertension and bradycardia may occur with non-selective beta-blocking drugs (e.g., Propranolol). Propranolol inhibits the bronchodilator effect of adrenaline.

Hypoglycaemic agents.

Adrenaline induced hyperglycaemia may lead to loss of blood sugar control in diabetic patients treated with hypoglycaemic agents.

Antidepressants

Tricyclic antidepressants and some other antidepressants inhibit reuptake of directly acting sympathomimetic agents, and may potentiate the effect of adrenaline, increasing the risk of development of hypertension and cardiac arrhythmias. Patients on monoamine oxidase inhibitors (MAOIs) should not receive sympathomimetic treatment.

Drugs potentiating hypokalaemic effects of adrenaline

The hypokalaemic effect of adrenaline may be potentiated by other drugs that cause potassium loss including corticosteroids, potassium depleting diuretics and aminophylline or theophylline; patients receiving high doses of beta 2-adrenergic agonists concomitantly should have their plasma potassium concentration monitored.

Other drugs

Some antihistamines and thyroid hormones may potentiate the effects of adrenaline, especially on heart rhythm and rate.

4.6 Fertility, pregnancy and lactation

Fertility

No data available.

Pregnancy Category A

Adrenaline has been given to 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. However, the use of adrenaline during labour is contraindicated because it may delay the second stage by inhibiting spontaneous or oxytocin induced contractions of the pregnant human uterus (see Sections 4.3 Contraindications and 4.5 Interactions with other medicines and other forms of interactions).

Lactation

Adrenaline is excreted in breast milk. The use of adrenaline in breastfeeding women is, therefore, not recommended.

4.7 Effects on ability to drive and use machines

No data available.

4.8 Undesirable effects

Metabolism and nutrition disorders

Anorexia, hypokalaemia, hyperglycaemia. Prolonged use or overdosage of adrenaline can result in severe metabolic acidosis.

Nervous system disorders

Headache, tremor, dizziness, impaired memory, psychomotor agitation.

Syncopal episodes have been reported in children.

Cerebrovascular or other haemorrhage and haemiplegia may result, especially in elderly patients.

Musculoskeletal and connective tissue disorders

In patients with Parkinsonian Syndrome, adrenaline increases rigidity and tremor.

Psychiatric disorders

Anxiety, fear, tenseness, restlessness, confusion, disorientation, hallucinations, irritability, , insomnia, psychosis may occur, psychiatric disorders may be exacerbated.

Cardiac disorders

Palpitations, tachycardia (sometimes with anginal pain) and cardiac arrhythmias may also occur along with hypertension which in some instances may induce reflex bradycardia as can vasodilation with flushing and hypotension. Ventricular fibrillation may occur and severe hypertension may lead to cerebral haemorrhage and pulmonary oedema. High doses may result in ventricular arrhythmia.

Respiratory, thoracic and mediastinal disorders

Dyspnoea, pulmonary oedema may occur after excessive doses and following aerosol application or in extreme sensitivity.

Gastrointestinal disorders

Nausea, vomiting, hypersalivation.

Vascular disorders:

Peripheral coldness.

Skin and subcutaneous tissue disorders

Flushing or redness of face and skin, sweating.

Renal and urinary disorders

Difficulty in micturition, urinary retention.

General disorders and administrative site conditions

Weakness, pallor.

Other

Inadvertent intravenous injection of adrenaline has also been reported to have caused convulsions, metabolic acidosis and renal failure with anuria.

Overdosage or inadvertent intravenous injection of usual subcutaneous doses of adrenaline may cause hypertension.

Repeated injections of adrenaline can cause necrosis as a result of vascular constriction at the injection site. Prolonged use or overdosage of adrenaline can result in severe metabolic acidosis.

Gas gangrene, which can be fatal, has been reported following intramuscular injection of adrenaline into the buttock or thigh. This appears to have been due to Clostridium organisms on the skin being deposited into muscle tissue during injection, with the vasoconstrictor properties of adrenaline enhancing the effects of the infection (see Section 4.2 Dose and method of administration).

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

Effects

Overdosage with adrenaline produces a rapid rise in blood pressure resulting in cerebral haemorrhage, cardiac arrhythmias leading to ventricular fibrillation and death, severe

hypertension leading to pulmonary oedema, which may also lead to death because of the peripheral constriction and cardiac stimulation produced.

Overdosage of adrenaline can result in severe metabolic acidosis because of elevated blood concentration of lactic acid.

Treatment

Combined alpha and beta adrenergic blocking agents such as labetalol may counteract the effects of adrenaline or a beta blocking agent may be used to treat supraventricular arrhythmias and phentolamine to control the alpha mediated effects on the peripheral circulation. Rapidly acting vasodilators such as nitrates and sodium nitroprusside may also be helpful.

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

Mechanism of action

Adrenaline is a direct-acting sympathomimetic agent exerting its effect on alpha and beta adrenoreceptors. Major effects are increased systolic blood pressure, reduced diastolic pressure, tachycardia, hyperglycaemia and hypokalaemia. It is a powerful cardiac stimulant. It has vasopressor properties, an antihistaminic action and is a bronchodilator. Its action is rapid in onset and of short duration.

5.2 Pharmacokinetic properties

Adrenaline is rapidly distributed to the heart, spleen, several glandular tissues and adrenergic nerves. It crosses the placenta and is excreted in breast milk. It is approximately 50% bound to plasma proteins. The onset of action is rapid and after intravenous infusion the half life is approximately 5-10 minutes.

Adrenaline is rapidly metabolised in the liver and tissues. Up to 90% of the IV dose is excreted as metabolites in the urine.

5.3 Preclinical safety data

Genotoxicity

Adrenaline and other catecholamines have been shown to have mutagenic potential *in vitro.* Adrenaline was positive in the *Salmonella* bacterial reverse mutation assay, positive in the mouse lymphoma assay, and negative in the *in vivo* micronucleus assay. Adrenaline is a mutagen based on the *E. coli* WP2 Mutoxitest bacterial reverse mutation assay.

Carcinogenicity

Long-term studies to evaluate the carcinogenic potential of adrenaline have not been conducted.

Reproductive and developmental toxicity

In animal reproduction studies, adrenaline demonstrated adverse developmental effects when administered to pregnant rabbits (gastroschisis), mice (teratogenic effects, embryonic lethality, and delayed skeletal ossification), and hamsters (embryonic lethality and delayed skeletal ossification) during organogenesis at doses approximately 15 times, 3 times and 2 times, respectively, the maximum recommended daily intramuscular or subcutaneous dose

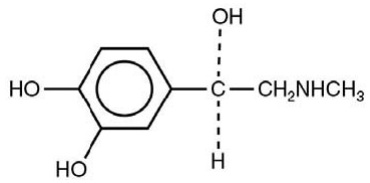
In a study in pregnant rabbits administered 1.2 mg/kg/day adrenaline (approximately 15 times the maximum recommended intramuscular or subcutaneous dose on a mg/m^2 basis) subcutaneously during organogenesis (on days 3 to 5, 6 to 7 or 7 to 9 of gestation), adrenaline caused teratogenic effects (including gastroschisis). Animals treated on days 6 to 7 had decreased number of implantations.

In a teratology study, pregnant mice were subcutaneously administered adrenaline (0.1 to 10 mg/kg/day) on Gestation Days 6 to 15. Teratogenic effects, embryonic lethality, and delays in skeletal ossification were observed at approximately 3 times the maximum recommended intramuscular or subcutaneous dose (on a mg/m^2 basis at maternal subcutaneous dose of 1 mg/kg/day for 10 days). These effects were not seen in mice at approximately 2 times the maximum recommended daily intramuscular or subcutaneous dose (on a mg/m^2 basis at a subcutaneous maternal dose of 0.5 mg/kg/day for 10 days).

Subcutaneous administration of adrenaline to pregnant hamsters at a dose of 0.5 mg/kg/day (approximately 2 times the maximum recommended intramuscular or subcutaneous dose on a mg/m^2 basis) on Gestation Days 7 to 10 resulted in delayed skeletal ossification and a reduction in litter size.

6. PHARMACEUTICAL PARTICULARS

The chemical structure of adrenaline is shown below.



The chemical formula is $C_9H_{13}NO_3$ and the molecular weight is 183.2.

CAS: 51-43-4; Melting point: 205°C to 212°C.

6.1 List of excipients

Sodium chloride, sodium metabisulfite, Water for injection.

6.2 Incompatibilities

Adrenaline is physically incompatible with alkalis, oxidising agents, copper, zinc, iron, silver and other metals.

Adrenaline has been reported to be incompatible with solutions containing the following: sodium warfarin, hyaluronidase aminophylline, sodium ampicillin, sodium amylobarbitone, ascorbic acid, potassium benzylpenicillin, calcium chloride, calcium gluconate, cephalothin, chloramphenicol sodium succinate, chlortetracycline hydrochloride, corticotrophin, diazepam, digitoxin, ergometrine maleate, erythromycin gluceptate, frusemide, hyaluronidase, hydrocortisone sodium succinate, methicillin sodium, nitrofurantoin, noradrenaline acid tartrate, sodium novobiocin, sodium pentobarbitone, procaine, prochlorperazine edisylate, promazine hydrochloride, sulfadiazine sodium, suxamethonium chloride, tetracycline hydrochloride, vancomycin hydrochloride, vitamin B complex with ascorbic acid; it forms polymers with sodium bicarbonate.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Store below 25°C. Protect from light. Do not use if the injection is brown or contains a precipitate.

6.5 Nature and contents of container

DBL Adrenaline 1:1,000 and 1:10,000 Solution for Injection is available in single use Type 1 glass ampoules in packs of 5 or 50.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MEDICINE SCHEDULE

Restricted Medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand, 1140.

Toll Free Number: 0800 736 363.

9. DATE OF FIRST APPROVAL

08 March 1984.

10. DATE OF REVISION OF TEXT

15 July 2021.

Summary table of changes

Section changed	Summary of new information
All	DBL Adrenaline 1:1000 and DBL Adrenaline 1:10000 Data Sheet merged into one Data Sheet
All	Minor editorial changes
4.3	Sensitivity to adrenaline excipients and use during labour and delivery
4.4	Precaution added for cerebrovascular insufficiency, angina pectoris, chronic lung disease, syncope, increases in rigidity and tremor from Parkinsonian Syndrome, diabetic patients, circulatory support, hypersensitivity to sodium metabisulfite, gangrene. Use in renal impairment and Use in elderly patients
4.5	Addition of warning that use during labour and delivery is contraindicated
4.6	Interaction between antihypertensive therapy, antidepressants and drugs potentiating hypokalaemic effects of adrenaline
4.8	Adverse events assigned by System Organ Class. New adverse evets added in the following SOC: Metabolism and nutrition disorders, Nervous system disorders, Musculoskeletal and connective tissue disorders, Psychiatric disorders, Cardiac disorders. Respiratory, thoracic and mediastinal disorders, Renal and urinary disorders , Injury, poisoning and procedural complications
5.2	Addition of preclinical safety information
6.2	Medicines that are incompatible with Adrenaline added.