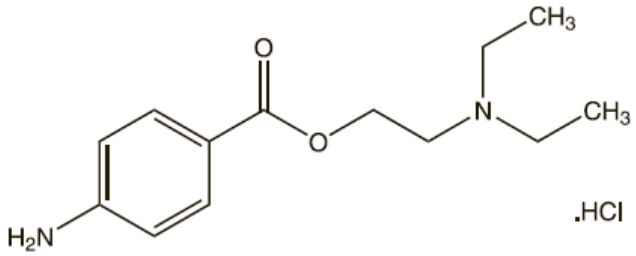
DBL™ Sterile Cardioplegia Concentrate

Name of the Medicine

Magnesium chloride hexahydrate
Potassium chloride
Procaine hydrochloride



Description

DBL™ Sterile Cardioplegia Concentrate is a sterile, clear, colourless solution, containing: magnesium chloride hexahydrate 3.25 grams, potassium chloride 1.19 grams, procaine hydrochloride 272.8 milligrams and water for injections to 20 mL. The pH is 4.0 to 6.0.

20 mL of the solution contains:	Magnesium chloride hexahydrate	16 mmol
	Potassium chloride	16 mmol
	Procaine hydrochloride	1 mmol

Magnesium chloride hexahydrate exists as colourless, odourless, deliquescent or hygroscopic crystals or flakes. It is very soluble in water, and freely soluble in alcohol. The chemical formula of magnesium chloride hexahydrate is $MgCl_2.6H_20$. Its molecular weight is 203.3 and its CAS Registry number is 7791-18-6.

Potassium chloride is a white crystalline or granular powder, or odourless, colourless, cubical, elongated or prismatic crystals. It is very soluble in water, and practically insoluble in alcohol and dehydrated alcohol. The chemical formula of potassium chloride is KCl. Its molecular weight is 74.55 and its CAS Registry number is 7447-40-7.

Procaine hydrochloride is a white crystalline powder, or small colourless or white odourless crystals. It is very soluble in water, soluble in alcohol, slightly soluble in chloroform, and practically insoluble in ether. The chemical formula of procaine hydrochloride is $C_{13}H_{20}N_2O_2$.HCl. Its molecular weight is 272.8 and its CAS Registry number is 51-05-8. For further detailed information on procaine hydrochloride, see the Product Information document on Procaine Hydrochloride Injection.

Pharmacology

Cardiac surgery is most easily performed while the heart is still and relaxed, in a bloodless environment. Cardioplegia solution is used, usually in combination with cardiac hypothermia, to produce rapid and complete diastolic arrest. Cardioplegia solution aims to minimise myocardial energy requirements during arrest, prevent ischaemic damage which may be caused by the absence of coronary blood flow during the arrest phase, and to minimise or prevent reperfusion injury when coronary blood flow is restored.

In addition to inducing and maintaining arrest, the chemical components of the cardioplegia solution can counteract the specific cellular effects of ischaemia, and the cellular events that may occur during reperfusion.

Magnesium prevents cellular potassium and magnesium loss, conserving magnesium for its role as an enzymatic cofactor. Magnesium appears to counteract the effects of calcium in excitation-contraction coupling, resulting in reduced energy consumption. Magnesium ions also have a weak arresting action on the heart.

Potassium induces rapid diastolic arrest by blocking the inward sodium current and initial phases of cellular depolarisation. Cellular energy stores (adenosine triphosphate and creatine phosphate) are thereby preserved for post-ischaemic activity.

Procaine has a protective effect on the myocardium. Laboratory studies in rats have shown this to be additive to the protective effects of potassium and magnesium. Procaine may help induce arrest and reduce reperfusion arrhythmias.

DBL™ Sterile Cardioplegia Concentrate must be diluted with Ringer's Injection before use, at a rate of 20 mL per litre (see **Dosage and Administration**). Ringer's Injection contains approximately 144 mmol/L of sodium ions, 4 mmol/L of potassium ions, 2 mmol/L of calcium ions and 152 mmol/L of chloride ions. Each litre of diluted cardioplegia solution will therefore contain approximately 144 mmol of sodium ions, 20 mmol of potassium ions, 2 mmol of calcium ions, 16 mmol of magnesium ions, 200 mmol of chloride ions and 1 mmol of procaine hydrochloride.

Calcium ions (contained in Ringer's Injection) help maintain the integrity of the cell membrane, and prevent the condition known as the "calcium paradox" from occurring during reperfusion.

Sodium ions (contained in Ringer's Injection) and *chloride* ions do not have a specific role in producing cardiac arrest, but result in a solution with a similar composition to that of normal extracellular fluid. Sodium ions are also essential for controlling calcium movements, and ensuring that intracellular calcium is kept at the diastolic resting level. The inclusion of sodium enables the electroneutral sodium-calcium exchange to be maintained.

The hyperosmolarity of the cardioplegia solution minimises the myocardial oedema which occurs during ischaemia and reperfusion.

Pharmacokinetics

DBL™ Sterile Cardioplegia Concentrate should not be absorbed systemically if it is used as recommended. However, systemic absorption could occur if large volumes of diluted cardioplegia solution are instilled and allowed to return to the heart lung machine without venting from the right heart.

Procaine is an ester type local anaesthetic which is poorly absorbed from mucous membranes, but is readily absorbed if it is administered parenterally. After absorption, it is rapidly hydrolysed by plasma cholinesterase to para-aminobenzoic acid and diethylaminoethanol; some may also be metabolised in the liver. About 80% of the para-aminobenzoic acid is excreted unchanged or conjugated in the urine. About 30% of the diethylaminoethanol is excreted in the urine, while the remainder is metabolised in the liver. Procaine is 6% bound to plasma proteins and less than 2% is excreted unchanged in the urine.

Magnesium salts are mainly excreted in the urine following parenteral administration. About 25 to 30% of magnesium is protein bound. Potassium is mainly excreted by the kidneys; it is secreted in the distal tubules in exchange for sodium or hydrogen ions. Some potassium is excreted in the faeces, and small amounts may also be excreted in sweat.

Indications

DBL™ Sterile Cardioplegia Concentrate is indicated for use in combination with ischaemia and hypothermia to induce cardiac arrest during open-heart surgery and to preserve the

myocardium during asystole.

Contraindications

DBL™ Sterile Cardioplegia Concentrate must not be used unless it has been diluted with Ringers Injection prior to use.

Use of DBL™ Sterile Cardioplegia Concentrate is contraindicated in patients who are hypersensitive to procaine.

As procaine is metabolised to produce para-aminobenzoic acid, it should be used with caution in patients who are allergic to para-aminobenzoic acid or its derivatives such as preservatives and sunscreens. Cross sensitivity can occur between procaine and other local anaesthetics of the para-aminobenzoic acid ester-type, para-aminobenzoic acid and hydroxybenzoate preservatives.

Procaine hydrochloride is contraindicated in patients:

- with low plasma cholinesterase levels or who are receiving anticholinesterases,
- with myasthenia gravis, severe shock or impaired cardiac conduction,
- receiving sulfonamides.

Precautions

DBL™ Sterile Cardioplegia Concentrate must be diluted with Ringer's Injection before use. Do not use the solution unless it is clear and free from particulate matter. Discard any unused portion.

Cardioplegia solution must not be administered by intravenous injection.
Cardioplegia solution should only be used for instillation into the coronary arteries during cardiopulmonary bypass, while the coronary circulation is isolated from the systemic circulation.

DBL™ Sterile Cardioplegia Concentrate should only be used by those who are trained in cardiac perfusion techniques and open heart surgery. Inotropic support drugs and appropriate defibrillation equipment should be readily available following use of the cardioplegia solution.

The cardioplegia solution should be cooled to 4°C prior to administration, thereby assisting in the reduction of cellular metabolism.

It is important to use sufficient cardioplegia solution (see **Dosage and Administration**) to ensure that the myocardium is evenly cooled. This especially applies to areas distal to arterial obstruction in patients with coronary artery disease. Inadequate dosage may result in uneven cooling, incomplete arrest and ischaemic injury.

Maintenance of hypothermia is critical. Myocardial temperature and activity should be monitored continuously throughout the procedure.

Plasma magnesium and potassium levels may rise if large volumes of diluted cardioplegia solution are instilled and allowed to return to the heart lung machine without any venting from the right heart. Therefore, right heart venting is recommended.

DBL™ Sterile Cardioplegia Concentrate should be used with caution in very young, elderly, acutely ill or debilitated patients, or patients with hyperthyroidism or other endocrine diseases, who may be more susceptible to the systemic toxicity of procaine.

DBL™ Sterile Cardioplegia Concentrate should also be used with caution in patients with reduced hepatic blood flow (such as in liver disease) or renal disease, since the risk of systemic toxicity is increased due to decreased clearance of procaine.

Procaine should be used with caution in patients with a genetic predisposition to malignant hyperthermia as the safety of local anaesthetic agents in these patients has not been fully established. A standard protocol for the management of malignant hyperthermia should be available.

Use in pregnancy (Category B2†)

Reproductive toxicity of DBL™ Sterile Cardioplegia Concentrate has not been studied in pregnant animals. It is known that procaine hydrochloride crosses the placenta. Magnesium and potassium are natural constituents of human tissues and fluids, and readily cross the placenta. The effect of DBL™ Sterile Cardioplegia Concentrate on the human foetus and reproductive capacity have not been established. DBL™ Sterile Cardioplegia Concentrate should be used in pregnant women only if unavoidable.

Use in lactation

It is not known whether procaine hydrochloride is distributed into breast milk. Magnesium and potassium are natural constituents of human tissues and fluids, and are distributed into breast milk. There are no studies in lactating animals. Due to lack of data, its use in breastfeeding women is not recommended.

Carcinogenicity, mutagenicity, impairment of fertility

Magnesium and potassium are natural constituents of human tissues and fluids, and no evidence of carcinogenic or mutagenic potential exists. No information is available on the carcinogenicity, mutagenicity or effect on fertility of procaine hydrochloride.

Interactions with other medicines

When used as recommended, systemic absorption of cardioplegia solution should not occur, and hence interactions between the cardioplegia solution and other medicines are unlikely. However, the following interactions could potentially occur if DBL™ Sterile Cardioplegia Concentrate is absorbed systemically:

Acetazolamide Acetazolamide may inhibit hydrolysis of procaine; concurrent administration may therefore theoretically extend the plasma half-life of procaine.

Anticholinesterase agents Anticholinesterase agents may inhibit procaine metabolism, leading to an increased risk of toxicity if procaine is used concurrently with anticholinesterase agents.

Antimyasthenic agents Procaine may antagonise the effects of antimyasthenic agents on skeletal muscle; concurrent use may, therefore, result in worsening of myasthenia gravis symptoms. Temporary dosage adjustment of antimyasthenic agents may be required.

CNS depressant medicines Concurrent use of procaine with CNS depressant medicines may result in enhanced CNS depressant effects.

Hyaluronidase Hyaluronidase may increase the diffusion rate of procaine hydrochloride, resulting in a decreased time of onset, but an increase in systemic toxicity.

Neuromuscular blocking agents Concurrent administration of procaine and neuromuscular blocking agents may prolong or enhance neuromuscular blockade. Magnesium salts may also interact with neuromuscular blocking agents.

Potassium-containing or potassium-sparing medicines Potassium salts should be used sparingly, if at all, in patients receiving medicines which increase serum potassium concentrations. Examples include potassium-sparing diuretics, angiotensin converting enzyme (ACE) inhibitors, cyclosporin, and potassium-containing medicines. Hyperkalaemia is more likely to occur in patients with renal impairment.

Sulfonamides Concurrent administration of procaine with sulfonamides may reduce the antibacterial action of the sulfonamide.

Incompatibilities
DBL™ Sterile Cardioplegia Concentrate is potentially incompatible with aminophylline, amylobarbitone sodium, chloramphenicol, chlorothiazide sodium, magnesium sulphate, nitrofurantoin, phenobarbitone sodium, pentobarbitone, phenytoin sodium, quinalbarbitone sodium, sodium bicarbonate, sodium iodide, sulfadiazine, thiopentone and amphotericin due to the presence of procaine hydrochloride.

Procaine hydrochloride is also reported to be incompatible with amphotericin B, alkali hydroxides and their carbonates, alkaline solutions and iodine.

Potassium chloride is reported to be physically incompatible with amphotericin B, diazepam, ergotamine tartrate, methylprednisolone sodium succinate and phenytoin sodium.

Potassium chloride is also potentially incompatible with mannitol.

Adverse Effects
The use of cardioplegia solution during cardiac surgery has been associated with a number of intraoperative and perioperative risks, including myocardial infarction, electrocardiograph (ECG) abnormalities and arrhythmias (including ventricular fibrillation). Cardioplegia solutions may cause potential electrolyte and acid-base abnormalities (e.g. hyperkalaemia). Patients undergoing cardiac surgery should therefore be monitored closely for any adverse effects.

Spontaneous recovery may be delayed or absent after circulation is restored following chemically-induced cardiac arrest. Defibrillation by electric shock may be required to restore normal cardiac function.

Plasma magnesium and potassium levels may rise if large volumes of cardioplegia solution are instilled and allowed to return to the heart lung machine without any venting from the right heart. This may lead to symptoms and signs of hypermagnesaemia and/or hyperkalaemia. This may lead to severe hypotension and metabolic acidosis (see **Precautions**).

See Product Information for Procaine Hydrochloride Injection for further information on adverse effects due to systemic absorption of procaine.

Dosage and Administration
DBL™ Sterile Cardioplegia Concentrate must be diluted with Ringer's Injection prior to use.
DBL™ Sterile Cardioplegia Concentrate or diluted cardioplegia solution must not be administered by intravenous injection.

It is important to use sufficient cardioplegia solution to ensure that the myocardium is evenly cooled (see **Precautions**).

The following information is intended as a guide only. Dosage may vary, depending on perfusion technique being used and the preference and experience of the surgeon. The volume of solution administered into the aortic root may vary depending on the duration or type of open heart surgical procedure.

DBL™ Sterile Cardioplegia Concentrate must be diluted before use, at a ratio of 20 mL to 1 litre of Ringer's Injection. The solution must be cooled to 4°C prior to use. Any unused portion should be discarded.

Following institution of cardiopulmonary bypass and cross clamping of the ascending aorta, the

cold, diluted cardioplegia solution is administered by rapid infusion into the aortic root. The solution may be administered at a rate of about 300 mL/m^2 body surface area/minute, over a period of about 2 to 4 minutes.

External cardiac cooling helps to ensure that the heart remains continuously cold. This can be achieved by infusing a cold physiological solution into the pericardial sac. Warmed solution can be removed by suction and replaced by cold solution to ensure maintenance of hypothermia.

If myocardial electromechanical activity persists or recurs, administration of cold cardioplegia solution may be repeated at a rate of about 300 mL/m^2/minute for a period of two minutes.

Diluted cardioplegia solution may be readministered every 20 to 30 minutes, or sooner if the myocardial temperature reaches 15 to 20°C, or if a return of cardiac activity is observed.

To reduce microbiological hazard, the solution should be used as soon as practicable after preparation. This product is for use in one patient only. Discard any remaining contents.

Overdosage

Excessive administration of cardioplegia solution may result in unnecessary dilation of coronary vessels and leakage into the perivascular myocardium, which may lead to tissue oedema. Any adverse effects should be treated symptomatically.

In case of overdose, immediately contact the Poisons Information Centre for advice (In Australia, call 13 11 26. In New Zealand, call 0800 764 766).

Presentation and Storage Conditions

DBL™ Sterile Cardioplegia Concentrate is supplied in 20 mL ampoules in a pack size of 5.

Store below 25°C. Protect from light.

Name and Address of Sponsor

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500 Collins Street
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Poison Schedule of the Medicine

Schedule 4 (Prescription Only Medicine)

Date of TGA Approval: 8 July 2003

Date of most recent amendment: 30 January 2012

† *Category B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformations or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.*

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