USER INFORMATION

INJECSOL CARDi

Sterile Cardioplegia Concentrated Injection

Sterile and Non-Pyrogenic

Composition:
Each 20 mL of solution contains:

Procaine Hydrochloride BP	272.8 mg (1 mmol)
Magnesium Hydrochloride $6H_2O$ BP	3.25 g (16 mmol)
Potassium Chloride BP	1.19 g (16 mmol)

Product Description:
INJECSOL CARDi (before and after dilution) is a clear and colourless solution.

Pharmacodynamics:
Mechanism of action
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.

INJECSOL CARDi must be diluted with Ringer's Injection before use, at a rate of 20 mL per litre. 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:
Absorption
INJECSOL CARDi 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.

Metabolism
After absorption, Procaine is rapidly hydrolysed by plasma cholinesterase to para-aminobenzoic acid and diethylaminoethanol; some may also be metabolised in the liver.

Excretion
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.

Indication:
INJECSOL CARDi 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.

Recommended Dosage:
Dosage
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.

The solution may be administered at a rate of about 300 mL/m² body surface area/minute, over a period of about 2 to 4 minutes.

Method of Administration
INJECSOL CARDi must be diluted with Ringer's Injection prior to use.
INJECSOL CARDi must not be administered by intravenous injection.

It is important to use sufficient INJECSOL CARDi to ensure that the myocardium is evenly cooled.

INJECSOL CARDi 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, INJECSOL CARDi is administered by rapid infusion into the aortic root.

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/m²/minute for a period of two minutes.

Diluted INJECSOL CARDi 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.

Route of Administration : Parenteral

Contraindications:
INJECSOL CARDi must not be used unless it has been diluted with Ringers Injection prior to use.

Use of INJECSOL CARDi 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.

Warnings and Precautions:
INJECSOL CARDi 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.

INJECSOL CARDi 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 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.

INJECSOL CARDi should be used with caution in acutely ill or debilitated patients, or patients with hyperthyroidism or other endocrine diseases, who may be more susceptible to the systemic toxicity 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 hepatic impairment
INJECSOL CARDi should also be used with caution in patients with reduced hepatic blood flow (such as in liver disease), since the risk of systemic toxicity is increased due to decreased clearance of procaine.

Use in renal impairment
INJECSOL CARDi should also be used with caution in patients with renal disease, since the risk of systemic toxicity is increased due to decreased clearance of procaine.

Use in the elderly
INJECSOL CARDi should be used with caution in elderly, who may be more susceptible to the systemic toxicity of Procaine.

Paediatric use
INJECSOL CARDi should be used with caution in very young, who may be more susceptible to the systemic toxicity of Procaine.

Effects on laboratory tests
No data available

Interactions with Other Medicaments:
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 INJECSOL CARDi 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.

Statement on usage during pregnancy and lactation:
Pregnancy
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 foetus having been observed.

Reproductive toxicity of INJECSOL CARDi 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 INJECSOL CARDi on the human foetus and reproductive capacity have not been established. INJECSOL CARDi should be used in pregnant women only if unavoidable.

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.

Adverse Effects/Undesirable 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.

Incompatibilities:
INJECSOL CARDi 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.

Symptoms and Treatment of Overdose:
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.

Storage Conditions Before and After Dilution:
Before Dilution: Do not store above 30°C
After Dilution: The solution should be used immediately after dilution and should be stored in refrigerator between 2°C to 8°C not exceeding 24 hours.

Shelf Life:
2 years from manufacturing date in the proposed storage condition. The solution should be used within 24 hours after dilution. Do not use after expiry.

Dosage forms and packaging available:
20 mL X 5 glass vials per box

Manufacturer/Product Registration Holder:

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