Approved Professional Information for Cardioplegic Induction Solution Fresenius and Cardioplegic Maintenance Solution Fresenius

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

Cardioplegic Induction Solution Fresenius 3,757 g/500 ml

Cardioplegic Maintenance Solution Fresenius 1,375 g/500 ml

Solutions for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CARDIOPLEGIC FRESENIUS FORMULATIONS

Content	**Induction Solution g/500 ml**	**Maintenance Solution g/500 ml**
Potassium chloride	3,757	1,375
Sodium chloride	0,777	0,735
Sodium citrate dihydrate	0,832	0,785
Citric acid monohydrate	0,104	0,098
or Citric acid anhydrous	0,095	0,08875
Sodium dihydrogen phosphate	0,079	0,075
Tris(hydroxymethyl)aminomethane (tromethamine)	4,548	4,28
Water for injection	to 500 ml	to 500 ml

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solutions for infusion.

Cardioplegic Induction Solution Fresenius: A clear, colourless solution.

Cardioplegic Maintenance Solution Fresenius: A clear, colourless to slightly yellow-coloured solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For blood cardioplegic cardiac bypass procedures.

4.2 Posology and method of administration

Posology

1. Both **Cardioplegic Fresenius** solutions are designed to be mixed with blood in the ratio of four parts blood and one part cardioplegic solution.
2. Add 35 ml of 50 % glucose injection BP per 500 ml **Cardioplegic Fresenius** solution using aseptic technique.
3. Discard after 24 hours following addition of glucose.

4. Cardioplegic Induction Solution Fresenius:

This high K^+ arresting solution is used and is given at 300 ml/min at 8 °C for three (3) minutes. Higher flow rates and longer infusion times may be necessary if the patient has mild aortic insufficiency.

5. Cardioplegic Maintenance Solution Fresenius:

This product is given every twenty (20) minutes or after the completion of each distal anastomosis when coronary artery bypass grafting is being performed.

The **Cardioplegic Fresenius** solution used is the low K^+ Maintenance solution and is given at a flow rate of 200 ml/min for two (2) minutes at 8 °C.

If retrograde cardioplegia is to be used, then one (1) minute of anterograde to the aortic root and grafts are given at 200 ml/min and one (1) minute of retrograde are given to the coronary sinus and grafts at 200 ml/min.

Method of administration

Intravenous infusion.

4.3 Contraindications

- Hypersensitivity to potassium chloride or to any of the excipients listed in section 6.1.
- Hyperchloremia and hyperkalaemia that are not related to the concentration effect associated with a volume depletion.
- Severe renal insufficiency (with oliguria/anuria).
- Uncompensated heart failure and severe congestive heart failure.
- Addison's disease.
- Fluid and sodium retention.
- Acute ischaemic stroke.
- Head trauma (first 24 hours).

4.4 Special warnings and precautions for use

Care must be taken that all **Cardioplegic Fresenius** solutions are mixed with blood in the ratio of four parts blood and one part cardioplegic solution (see section 4.2).

Add 35 ml of 50 % glucose injection BP per 500 ml **Cardioplegic Fresenius** solution before administration (see section 4.2).

Potassium should be administered with considerable care to patients with cardiac disease or conditions predisposing to hyperkalaemia such as renal or adrenocortical insufficiency, acute dehydration, or extensive tissue destruction as occurs with severe burns. Regular monitoring of clinical status, serum electrolytes and ECG is advisable in patients receiving potassium therapy, particularly those with cardiac or renal impairment.

Sodium salts should be administered with caution to patients with hypertension, heart failure, peripheral or pulmonary oedema, impaired renal function, pre-eclampsia, or other conditions associated with sodium retention (see section 4.5).

Hyponatraemia

Patients with non-osmotic vasopressin release (e.g. in acute illness, pain, post-operative stress, infections, burns, and CNS diseases), patients with heart-, liver- and kidney diseases and patients exposed to vasopressin agonists (see section 4.5) are at particular risk of acute hyponatraemia upon infusion of hypotonic fluids.

Acute hyponatraemia can lead to acute hyponatraemic encephalopathy (brain oedema) characterised by headache, nausea, seizures, lethargy and vomiting. Patients with brain oedema are at particular risk of severe, irreversible and life-threatening brain injury.

Children, women in the fertile age and patients with reduced cerebral compliance (e.g. meningitis, intracranial bleeding, and cerebral contusion) are at particular risk of the severe and life-threatening brain swelling caused by acute hyponatraemia.

Paediatric population

The infusion rate and volume depends on the age, weight, clinical and metabolic conditions of the patient, concomitant therapy, and should be determined by a doctor experienced in paediatric intravenous fluid therapy.

Children (including neonates and older children) are at increased risk of developing hyponatraemia as well as for developing hyponatraemic encephalopathy.

The infusion of hypotonic fluids together with the non-osmotic secretion of ADH may result in hyponatraemia.

Plasma electrolyte concentrations should be closely monitored in the paediatric population as this population may have impaired ability to regulate fluids and electrolytes.

Rapid correction of hyponatraemia is potentially dangerous (risk of serious neurologic complications). Dosage, rate, and duration of administration should be determined by a doctor experienced in paediatric intravenous fluid therapy.

In order to avoid potentially fatal over infusion of intravenous fluids to the neonate, special attention needs to be paid to the method of administration. When using a syringe pump to administer intravenous fluids or medicines to neonates, a bag of fluid should not be left connected to the syringe.

When using an infusion pump all clamps on the intravenous administration set must be closed before removing the administration set from the pump, or switching the pump off. This is required regardless of whether the administration set has an anti free flow device.

The intravenous infusion device and administration equipment must be frequently monitored.

Geriatric population

When selecting the type of infusion solution and the volume/rate of infusion for a geriatric patient, consider that geriatric patients are generally more likely to have cardiac, renal, hepatic, and other diseases or concomitant medicine therapy.

Cardioplegic Fresenius solutions contain sodium.

Cardioplegic Induction Solution Fresenius contains 306 mg sodium per 500 ml, equivalent to 15,3 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Cardioplegic Maintenance Solution Fresenius contains 289 mg sodium per 500 ml, equivalent to 14,5 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

Caution is advised in patients treated with lithium. Renal sodium and lithium clearance may be increased during administration of **Cardioplegic Fresenius** solutions and can result in decreased lithium levels.

Cardioplegic Fresenius solutions should be used with caution in patients treated concurrently or recently with medicines that can cause hyperkalaemia or increase the risk of hyperkalaemia, such as potassium sparing diuretics (e.g. amiloride, spironolactone, triamterene).

Administration of potassium in patients treated with such medicines is associated with an increased risk of severe and potentially fatal hyperkalaemia, in particular in the presence of other risk factors for hyperkalaemia.

Regarding medicines (such as certain antiepileptic and psychotropic medications) that increase the risk of hyponatraemia or sodium and fluid retention, see section 4.4.

Medicines leading to an increased vasopressin effect

The below listed medicines increase the vasopressin effect, leading to reduced renal electrolyte free water excretion and increase the risk of hospital acquired hyponatraemia following inappropriately balanced treatment with i.v. fluids (see sections 4.4 and 4.8).

- Medicines stimulating vasopressin release, e.g. chlorpropamide, clofibrate, carbamazepine, vincristine, selective serotonin reuptake inhibitors, 3.4-methylenedioxy-N-methamphetamine, ifosfamide, antipsychotics, narcotics.
- Medicines potentiating vasopressin action, e.g. chlorpropamide, NSAIDs, cyclophosphamide.
- Vasopressin analogues, e.g. desmopressin, oxytocin, terlipressin.

Other medicines increasing the risk of hyponatraemia also include diuretics in general and antiepileptics such as oxcarbazepine.

Solutions containing potassium should be used with caution in patients receiving medicines that increase serum potassium concentrations (potassium-sparing diuretics, ACE inhibitors, cyclosporin, and medicines that contain potassium such as potassium salts of penicillin).

Corticosteroids are associated with the retention of sodium and water, with oedema and hypertension.

4.6 Fertility, pregnancy and lactation

The safety of **Cardioplegic Fresenius** solutions in pregnancy and lactation has not been established.

4.7 Effects on ability to drive and use machines

There is no information on the effects of **Cardioplegic Fresenius** solutions on the ability to drive and use machines.

4.8 Undesirable effects

a) Summary of the safety profile

Hyperkalaemia may occur. The most serious effects of hyperkalaemia are disturbances in cardiac conduction, arrhythmias, hypotention and muscle weakness (see sections 4.4 and 4.9).

Hyponatraemia may occur and can lead to CNS manifestations including seizures, coma, cerebral oedema and death (see sections 4.4 and 4.9).

b) Tabulated summary of adverse reactions

System organ class	**Adverse reaction** **Frequency unknown** (cannot be estimated from the available data)
Immune system disorders	Anaphylactic reaction Hypersensitivity
Metabolism and nutrition disorders	Hospital acquired hyponatraemia* Hyperkalaemia Hypervolaemia
Nervous system disorders	Hyponatraemic encephalopathy*
Cardiac disorders	Cardiac arrest**

Vascular disorders	Phlebitis Venous thrombosis Thrombophlebitis
Skin and subcutaneous tissue disorders	Rash Pruritis
General disorders and administrative site conditions	Infusion site pain Injection site vesicles Injection site infection Extravasation Chills Pyrexia Sweating

* Hospital acquired hyponatraemia may cause irreversible brain injury and death due to development of acute hyponatraemic encephalopathy (see section 4.4).

** As a manifestation of rapid intravenous administration and/or of hyperkalaemia.

c) Description of selected adverse reactions

Incorrect administration technique might cause the appearance of fever reactions such as chills and sweating.

Injection site reactions include infusion site pain, injection site vesicles, injection site infection and extravasation.

d) Paediatric population

Children (including neonates and older children) are at increased risk of developing hyponatraemia as well as for developing hyponatraemic encephalopathy (see section 4.4).

e) Other special populations

Children, women in the fertile age and patients with reduced cerebral compliance (e.g. meningitis, intracranial bleeding, and cerebral contusion) are at particular risk of the severe and life-threatening brain swelling caused by acute hyponatraemia (see section 4.4).

When selecting the type of infusion solution and the volume/rate of infusion for a geriatric patient, consider that geriatric patients are generally more likely to have cardiac, renal, hepatic, and other diseases or concomitant medicine therapy (see section 4.4).

Reporting of suspected adverse reactions

Health care providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

Reporting suspected adverse reactions after authorisation of Cardioplegic Fresenius solutions is important. It allows continued monitoring of the benefit/risk balance of Cardioplegic Fresenius solutions. Health care providers are asked to report any suspected adverse reactions via the Adverse Drug Reaction Reporting Form, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Excess administration of **Cardioplegic Fresenius** solutions can cause:

- Adverse effects on water and electrolyte balance with corresponding complications. Severe dilutional hyponatraemia and its complications can be fatal.
- Hyponatraemia (which can lead to CNS manifestations including seizures, coma, cerebral oedema and death).
- Fluid overload (which can lead to central and/or peripheral oedema).

- Hyperkalaemia. If hyperkalaemia is present or suspected, discontinue the infusion immediately and institute close ECG, laboratory and other monitoring and, as necessary, corrective therapy to reduce serum potassium levels. Manifestations of hyperkalaemia may include:
  - disturbances in cardiac conduction and arrhythmias, including bradycardia, heart block, asystole, ventricular tachycardia, ventricular fibrillation
  - hypotension
  - muscle weakness up to and including muscular and respiratory paralysis, paraesthesia of extremities, gastrointestinal symptoms (ileus, nausea, vomiting, abdominal pain).
- Arrhythmias and conduction disorders. In addition, the ECG shows progressive changes that occur with increasing potassium levels. Possible changes include:
  - peaking of T waves,
  - loss of P waves, and
  - QRS widening.

  However, the correlation between potassium levels and ECG changes is not precise, and whether or at which potassium level certain ECG signs develop depends on factors such as patient sensitivity, the presence of other electrolyte disorders, and the rapidity of the development of hyperkalaemia. The presence of any ECG findings that are suspected to be caused by hyperkalaemia should be considered a medical emergency.

See also sections 4.4 and 4.8

When assessing an overdose, any additives in the solution must also be considered.

Clinically significant overdose of **Cardioplegic Fresenius** solutions may, therefore, constitute a medical emergency.

Interventions include discontinuation of **Cardioplegic Fresenius** solutions, dose reduction and other measures as indicated for the specific clinical constellation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 24 - Mineral substitutes, electrolytes.

Pharmacotherapeutic group: Electrolyte solutions.

ATC code: B05XA03.

Cardioplegic Fresenius solutions are hypotonic.

The primary action of **Cardioplegic Fresenius** solutions is dependent on the concentration of the potassium ion (K^+) resulting in depolarisation of the cardiac muscle and cessation of contractile function. The presence of buffers in combination with K^+ counteracts the intracellular acidosis resulting from cardiac arrest. Energy substrates such as glucose and gluconeogenic precursor amino acids are included to provide cellular energy during the phase of anaerobic metabolism associated with cessation of contractile function.

5.2 Pharmacokinetic properties

Factors influencing potassium transfer between intracellular and extracellular fluid such as acid-base disturbances can distort the relationship between plasma concentrations and total body stores. Potassium is excreted mainly by the kidneys; it is secreted in the distal tubules in exchange of sodium or hydrogen ions. The capacity of the kidneys to conserve potassium is poor and some urinary excretion of potassium continues even when there is severe

depletion. Some potassium is excreted in the faeces and small amounts may also be excreted in sweat.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride (osmotic agent)

Sodium citrate dihydrate

Citric acid monohydrate or Citric acid anhydrous

Sodium dihydrogen phosphate

Tris(hydroxymethyl)aminomethane (tromethamine)

Water for injection

Hydrochloric acid (for pH-adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, it is the responsibility of the doctor to judge the incompatibility of an additive medicine with **Cardioplegic Fresenius** solutions by checking for eventual colour change and/or eventual precipitate, insoluble complexes or crystal apparition.

The Professional Information of the medicine to be added must be consulted.

When a medicine is added, the solution must be administered immediately.

As a guidance, the following medicines are incompatible with **Cardioplegic Fresenius** solutions (non-exhaustive listing):

- Amphotericin B
- Dobutamine

Those additives known to be incompatible should not be used.

6.3 Shelf life

Cardioplegic Induction Solution Fresenius: 12 months

Cardioplegic Maintenance Solution Fresenius: 24 months

In-use shelf life:

To be used immediately after the bag is opened.

6.4 Special precautions for storage

Store at or below 25 °C.

Discard any unused portion.

For storage of the opened product, see section 6.3.

6.5 Nature and contents of container

1, 18 or 20 x 500 ml freeflex (polyolefine) bags

24 x 500 ml PVC bags.

Not all container types and pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Discard any unused portion.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi Manufacturing SA (Pty) Ltd

6 Gibaud Road

Korsten, 6020

Port Elizabeth

South Africa

8. REGISTRATION NUMBER

Cardioplegic Induction Solution Fresenius 30/24/0133

Cardioplegic Maintenance Solution Fresenius 30/24/0134

9. DATE OF FIRST AUTHORISATION

21 December 2000

10. DATE OF REVISION OF THE TEXT

01 April 2022