PLEGISOL

cardioplegic solution for cardiac perfusion (intracoronary administration)

1000 ml Bag for infusion

Reference market: US

Saudi Arabia

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PLEGISOL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sodium chloride ..... 6.430 g

Calcium chloride ..... 0.176 g

Magnesium chloride ..... 3.253 g

Potassium chloride ..... 1.193 g

For 1,000 ml.

Sodium: 110 mmol/litre

Potassium: 16 mmol/litre

Chloride: 160 mmol/litre

Magnesium: 16 mmol/litre

Calcium: 1.2 mmol/litre

Osmolarity: 260 mOsm/litre

For the full list of the excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cardioplegic solution for cardiac perfusion (intracoronary administration)

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Plegisol (Cardioplegic Solution) when suitably buffered in combination with ischemia and hypothermia is used to induce cardiac arrest during open heart surgery.

4.2. Posology and method of administration

Posology

The following information is suggested as a guide and is subject to variation according to the preference and experience of the surgeon.

It is required that 10 mL (840 mg) of 8.4% Sodium Bicarbonate Injection, USP (10 mEq each of sodium and bicarbonate) be added aseptically and thoroughly mixed with each 1000 mL of cardioplegic solution to adjust pH. **Use 10 mL of Hospira List 4900, 8.4% Sodium Bicarbonate Injection, USP, to achieve the approximate pH of 7.8 when measured at room temperature. Use of any other Sodium Bicarbonate Injection may not achieve this pH due to the varying pH's of Sodium Bicarbonate Injections.** Due to its inherent instability with other components, sodium bicarbonate must be added just prior to administration. After this addition, the solution must be used within 24 hours. The solution should be cooled to 4°C prior to use.

Following institution of cardiopulmonary bypass at perfusate temperatures of 28° to 30°C, and after cross-clamping of the ascending aorta, the buffered solution is administered by rapid infusion into the aortic root. The initial rate of infusion may be 300 mL/m^2/minute (about 540 mL/min in a 5'8", 70 kg adult with 1.8 square meters of surface area) given for a period of two to four minutes. Concurrent external cooling (regional hypothermia of the pericardium)

may be accomplished by instilling a refrigerated (4°C) physiologic solution such as Normosol®-R (balanced electrolyte replacement solution) or Ringer's Injection, USP into the chest cavity.

Should myocardial electromechanical activity persist or recur, the solution may be reinfused at a rate of 300 mL/m^2/min for a period of two minutes. Reinfusion of the solution may be repeated every 20 to 30 minutes or sooner if myocardial temperature rises above 15° to 20°C or returning cardiac activity is observed. The regional hypothermia solution around the heart also may be replenished continuously or periodically in order to maintain adequate hypothermia. Suction may be used to remove warmed infusates. An implanted thermistor probe may be used to monitor myocardial temperature.

The volumes of solution instilled into the aortic root may vary depending on the duration or type of open heart surgical procedure.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit (See 4.4 Special warnings and precautions).

Method of administration

To Open

Tear outer wrap at notch and remove solution container. If supplemental medication is desired, follow directions below before preparing for administration. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

To add 10 mL of 8.4% Sodium Bicarbonate Injection, USP, Hospira List 4900, and other supplemental medication, follow directions below before preparing for administration.

To Add Medication

1. Prepare additive port.
2. Using aseptic technique and an additive delivery needle of appropriate length, puncture resealable additive port at target area, inner diaphragm and inject. Withdraw needle after injecting medication.
3. The additive port may be protected by covering with an additive cap.
4. Mix container contents thoroughly.

Preparation for Administration
(Use aseptic technique)

1. Close flow control clamp of administration set.
2. Remove cover from outlet port at bottom of container.
3. Insert piercing pin of administration set into port with a twisting motion until the set is firmly seated. **NOTE:** See full directions on administration set carton.
4. Suspend container from hanger.
5. Squeeze and release drip chamber to establish proper fluid level in chamber.
6. Attach aortic infusion device to set.
7. Open flow control clamp to expel air from set and aortic infusion device. Close clamp.
8. Position aortic infusion device to introduce solution into aortic root.

9. Regulate rate of administration with flow control clamp.

4.3. Contraindications

- Plegisol must not be administered without the addition of 8.4% Sodium Bicarbonate Injection, USP,
- Hospira List 4900**.**
- **NOT FOR INTRAVENOUS INJECTION.**
  This solution is only for instillation into cardiac vasculature after buffering with sodium bicarbonate.

4.4. Special warnings and precautions for use

This solution should be used only by those trained to perform open heart surgery. This solution is intended only for use during cardiopulmonary bypass when the coronary circulation is isolated from the systemic circulation (See **4.1 Therapeutic indications**).

Do not instill the solution into the coronary vasculature unless sodium bicarbonate has been added. If large volumes of cardioplegic solution are infused and allowed to return to the heart lung machine without any venting from the right heart, then plasma magnesium and potassium levels may rise. Development of severe hypotension and metabolic acidosis while on bypass has been reported when large volumes (8 to 10 liters) of solution are instilled and allowed to enter the pump and then the systemic circulation. Right heart venting is therefore recommended. The buffered solution with added sodium bicarbonate should be cooled to 4°C prior to administration and used within 24 hours of mixing.

PRECAUTIONS

Myocardial temperature should be monitored during surgery to maintain hypothermia.
Continuous electrocardiogram monitoring is essential to detect changes in myocardial activity during the procedure.

Appropriate equipment to defibrillate the heart following cardioplegia should be readily available.
Inotropic support drugs should be available during postoperative recovery.

Do not administer unless solution is clear and container is undamaged. Discard unused portion.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established. Because of differences in structure, function, and metabolism, clinical myocardial protection strategies and Cardioplegia solutions that are effective in adult hearts may be less effective in the immature heart.

Geriatric Use
Clinical studies of Plegisol did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between older and younger patients.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosage range reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease.

This product is unique in that there is no hepatic or renal excretion and specific adjustments for dosing in the elderly are not known.

4.5. Interaction with other medicinal products and other forms of interaction

Additives may be incompatible. Consult with pharmacist, if available. When introducing additives, use aseptic technique, mix thoroughly and do not store (See **4.2 Posology and method of administration**).

4.6. Fertility, pregnancy and lactation

Pregnancy

Animal reproduction studies have not been conducted with Plegisol. It is also not known whether this solution can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Plegisol should be given to a pregnant woman only if clearly needed.

4.7. Effects on ability to drive and use machines

Not applicable.

4.8. Undesirable effects

Intraoperative and perioperative potential hazards of open heart surgery include myocardial infarction, electrocardiographic abnormalities, and arrhythmias, including ventricular fibrillation. Spontaneous recovery after cardioplegic cardiac arrest may be delayed or absent when circulation is restored. Defibrillation by electric shock may be required to restore normal cardiac function.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after market authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system .

To Report side effects

- Saudi Arabia

National Pharmacovigilance and Drug Safety Centre (NPC)
- Call NPC at +966-11-2038222, Ext 2317-2356-2340
- Call center : 19999
- Fax: +966 11 205 7662
- E-mail: npc.drug@sfda.gov.sa
- Website: https://ade.sfda.gov.sa/

Other GCC States

- *Please contact the relevant competent authority.*

4.9. Overdose

Overzealous instillation of the solution may result in unnecessary dilatation of the myocardial vasculature and leakage into the perivascular myocardium, possibly causing tissue edema (See 4.4 special **warnings and precautions,** and 4.8 **undesirable effects**).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Plegisol (Cardioplegic Solution) is a sterile, nonpyrogenic, essentially isotonic, formulation of electrolytes in water for injection. It is a "core solution" intended for use ***only after addition of sodium bicarbonate*** to adjust pH prior to administration. After buffering with sodium bicarbonate it is suitable for cardiac instillation (usually with hypothermia) to induce arrest during open heart surgery. Other agents may be added to the solution prior to instillation (*See 4.2 posology and method of admiration*).

Plegisol with added sodium bicarbonate when cooled and instilled into the coronary artery vasculature, causes prompt arrest of cardiac electromechanical activity, combats intracellular ion losses and buffers ischemic acidosis. When used with hypothermia and ischemia, the action may be characterized as cold ischemic potassium-induced cardioplegia. This is conducive to providing the surgeon with a quiet, relaxed heart and bloodless field of operation.

Calcium (Ca^{++}) ion in low concentration is included in the solution to maintain integrity of cell membrane to ensure that there is no likelihood of calcium paradox during reperfusion.

Magnesium (Mg^{++}) ion may help stabilize the myocardial membrane by inhibiting a myosin phosphorylase, which protects adenosine triphosphate (ATP) reserves for postischemic activity. The protective effects of magnesium and potassium have been shown to be additive.

Potassium (K^{+}) ion concentration is responsible for prompt cessation of mechanical myocardial contractile activity. The immediacy of the arrest thus preserves energy supplies for postischemic contractile activity in diastole.

The chloride (Cl^{-}) and sodium (Na^{+}) ions have no specific role in the production of cardiac arrest. Sodium is essential to maintain ionic integrity of myocardial tissue. The chloride ions are present to maintain the electroneutrality of the solution.

Added bicarbonate (HCO_3^{-}) anion is included as a buffer to render the solution slightly alkaline and compensate for the metabolic acidosis that accompanies ischemia.

Extemporaneous alternative buffering to the described formulation of this solution is not recommended.

5.2. Pharmacokinetic properties

Not documented.

5.3. Preclinical safety data

Not documented.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Hydrochloric acid or sodium hydroxide, Nitrogen, water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3. Shelf life

Before opening: 2 years

After opening: 24 hours after opening of the bag.

6.4. Special precautions for storage

- Do not freeze.
- Store below 25 °C.

6.5. Nature and contents of container

1,000 ml bag (plasticised PVC).

6.6. Special precautions for disposal and other handling

No special requirements.

7. FURTHER INFORMATION

MARKETING AUTHORISATION HOLDER

Hospira Inc, Lake Forest, United states

MANUFACTURER

ICU medical Fleet Services LLC (Previously Hospira Inc), Austin, United States.

8. MARKETING AUTHORISATION NUMBER(S)

54-549-91

9. DATE FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12-Jun-1991

10. DATE OF REVISION OF THE TEXT

April 2018

11- Dosimetry

N/A.