Servator® C SALF
Cold storage solution

DIRECTIONS FOR PREPARATION AND USE

Not for Direct Injection or Intravenous Use (Single Use Only)
Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

DESCRIPTION

Servator® C SALF can be used for hypothermic cardiac flushing and storage in preparation for transportation and eventual transplantation of the heart into the recipient. The quantitative composition of Servator® C SALF is:

Mannitol	60 mmol
Lactobionic acid	80 mmol
Glutamic acid	20 mmol
Histidine	30 mmol
Calcium chloride	0.25 mmol
Potassium chloride	15 mmol
Magnesium chloride	13 mmol
Sodium hydroxide	100 mmol
Reduced glutathione	3 mmol
Water for injections q.s. to 1000 ml	

Servator® C SALF is a clear to slightly yellow, sterile, non-pyrogenic, extracellular solution for hypothermic flushing and storage of hearts. The solution is slightly alkaline (pH 7.3 ± 0.2 at 20°C), slightly hypertonic (approximate calculated osmolarity 242-368 mOsmol/L) with low viscosity (1.15 cSt), and has a high buffering capacity (acidic approximately 11 mmol, alkaline approximately 7 mmol). After removal from refrigerated storage (2°- 8°C or 36°- 46°F), the cold solution is used to flush the heart immediately before removal from the donor and/or immediately after removal from the donor. The solution is left in the organ vasculature during hypothermic storage and transportation. This solution is to be used for cold storage of hearts and not for continuous machine perfusion. Administration of the solution at the recommended temperatures will effectively cool the heart and should reduce its metabolic requirements.

INTENDED USE

Servator® C SALF is intended for flushing and cold storage of hearts at the time of their removal from the donor in preparation for storage, transportation, and eventual transplantation into a recipient.

CONTRAINDICATIONS

There are no known contraindications when used as directed.

WARNINGS

Servator® C SALF should only be used in conjunction with cardiac transplantation (flushing and cold storage).

- NOT for in vivo use
- NOT for direct systemic injection
- NOT for intravenous infusion
- NOT for continuous perfusion
- For single use only

Before perfusion is established in the recipient, the donor heart MUST BE flushed free of the cold storage solution using a physiological solution to prevent occurrence in the recipient of potentially serious cardiovascular complications such as hyperkalemic cardiac arrest or bradyarrhythmia.

Improper handling of materials may lead to contamination of the cardiac allograft.

Incorrect attachment of the tubing set may result in leakage from container.

PRECAUTIONS

Servator® C SALF includes drug components which, individually, may cause hypersensitivity reactions in patients. Physicans should consult individual labeling and be alert to treat possible reactions.

- The use of Servator® C SALF in pediatric patients has not been studied
- DO NOT USE the solution if it has been frozen at any time
- Servator® C SALF MUST NOT be injected systemically
- DO NOT USE the solution if particulate matter, precipitates, or contamination is evident in the solution
- Check the bag for leaks by squeezing the container firmly. If leak(s) arefound, discard the solution container(s)
- Servator® C SALF should not be diluted at any time
- Supplemental substances must not be added to the Servator® C SALF solution
- DO NOT INGEST
- DO NOT USE beyond expiration date

ADVERSE REACTIONS

Since Servator® C SALF is not administered systemically to a heart donor or recipient, the solution should not interact with medications normally given to this type of patient or cause specific adverse reactions due to systemic administration.

In a large North American clinical trial comparing Servator® C SALF with conventional solutions (Control), 64 cardiac allograft recipients exposed to Servator® C SALF were included in the intent to treat analysis. Two serious adverse events were considered possibly related to Servator® C SALF: fluid overload (n=1) and right ventricular dysfunction (n=1). Adverse events that occurred in ≥10% of patients in each treatment group are listed by body system and individual adverse event in the following table.

Body System Individual Adverse Event	**Servator® C SALF Group (n = 64)**	**Control Group (n = 67)**
Cardiac System	42 (66%)	46 (69%)
Rejection	20 (31%)	25 (37%)
Cardiovascular disorder	7 (11%)	9 (13%)
Atrial fibrillation	9 (14%)	5 (7%)
Hypotension	7 (11%)	5 (7%)
Arrhytmia	7 (11%)	3 (4%)
Cardiovascular System	13 (20%)	10 (15%)
Hypertension	9 (14%)	5 (7%)
Body as a Whole	23 (36%)	18 (27%)
Fever	7 (11%)	3 (4%)
Respiratory System	16 (25%)	18 (27%)
Metabolic and Nutritional	13 (20%)	17 (25%)
Nervous System	11 (17%)	14 (21%)
Urogenital System	17 (27%)	12 (18%)
Kidney function abnormal	7 (11%)	5 (7%)
Digestive System	12 (19%)	12 (18%)
Hematological and Lymphatic Systems	15 (23%)	14 (21%)
Coagulation Disorder	6 (9%)	8 (12%)

CLINICAL STUDIES

Three worldwide clinical studies with a total of 253 patients (160 Servator® C SALF, 93 Control) have evaluated Servator® C SALF for flushing and cold storage of hearts in preparation for storage, transportation, and transplantation.

1. Multicenter, Randomized, Controlled Evaluation of Servator® C SALF vs. Standard Control Solutions (North America - same study as referenced in the "Adverse Reactions" section above).

This was a multicenter, randomized, controlled, open label comparison of Servator® C SALF to standard preservation solutions conducted in the United States and Canada. Primary endpoint was 7 day patient survival. Additional safety and efficacy evaluation included 30 day patient survival, 30 day graft survival, adverse events, cardiopulmonary bypass weaning, time to independent cardiac function, pacing requirement, ECG evaluation, and graft function. The study enrolled 133 patients (65 Servator® C SALF, 68 Control), 21-68 years of age, 82% male/18% female, and 80% Caucasian. One patient from each group did not receive a transplant after randomization and was excluded from analysis.

Therefore, the intent to treat analysis included 64 patients in the Servator® C SALF group and 67 patients in the Control group. Mean ± SD total and cold ischemic times for the cardiac allografts were 3.3 ± 1.0 hour and 97 ± 73 minutes, respectively, for the Servator® C SALF group, and 3.1 ± 1.0 hour and 96 ± 76 minutes, respectively, for the Control group.

Results:
Patient and graft survival at Day 7 and Day 30 posttransplant are summarized in the following table.

	Servator C SALF (n = 64)	Control (n = 67)
Patient survival Day 7	97%	94%
Day 30	94%	88%
Graft survival Day 7	97%	91%
Day 30	94%	87%
Serious adverse events (overall)	38%	46%
Serious adverse events (cardiac related)	13% *	25%

* Statistically significant by 95% (one sided) confidence interval analysis

- Similar adverse event and clinical laboratory profiles between treatment groups
- Of 12 deaths in this study (4 Servator C SALF, 8 control), 2 deaths possibly related to study solution (1 Servator C SALF, right ventricular dysfunction; 1 control, right heart failure)

Conclusion:
Servator C SALF was shown to be equivalent to the various standard solutions evaluated in this trial.

2. Single Center, Randomized, Controlled Comparison of Servator C SALF vs. Custodiol® Solution (Austria).

This trial was a comparative evaluation of Servator C SALF versus Custodiol. Primary efficacy endpoint was the rate of spontaneous defibrillation after weaning from cardiovascular bypass. Safety and secondary efficacy parameters included hemodynamic parameters and clinical evaluation, histopathology, adverse events and death. The study enrolled 50 patients, 25 per treatment arm.

Results:
- The Servator C SALF group had a higher rate of spontaneous defibrillation (80% vs. 36%; p=0.002, Chi-Square test)
- Frequencies of serious adverse events, death, and rate of acute graft failure were comparable between groups
- 2 deaths in each treatment arm, none attributed to Servator C SALF

3. Multicenter, Open Label, Non Controlled Evaluation of Servator C SALF for Cardiac Preservation (France).

This was a multicenter, open label, non controlled evaluation of the quality of myocardial preservation of Servator C SALF. Efficacy and safety parameters included evaluation of spontaneous defibrillation, perioperative hemodynamics, clinical evaluation, 1 month mortality, and adverse events. The study enrolled 70 patients.

Results:
- 53% of the grafts defibrillated spontaneously
- 1 month mortality rate was 8.6% (6/70 patients)
- The most common adverse events were cardiac (19 cases), infectious (17 cases), renal (7 cases), and neurological (5 cases)

4. Early Studies

Two clinical trials in France compared Servator C SALF to standard preservation solutions for flushing and cold storage of hearts in preparation for transplantation. These studies used a 2 component Servator C SALF system, in which the reduced glutathione was supplied in a separate container to be added immediately prior to use. The studies enrolled 65 adult patients (33 Servator C SALF, 32 control), 85% male. Data from these two trials revealed no significant differences in the frequency of cardiac, renal, pulmonary, infectious, or non specific adverse events.

PREPARATION AND ADMINISTRATION

- Remove solution from refrigerated storage, making sure solution is not frozen
- Remove outer plastic overwrap prior to use
- Discard the oxygen absorber sachet
- Label side of the bag should be facing toward you in preparation for administration
- The 2 exit ports should be extended from the bag
- Pull the tab on the port and completely remove the protective cap from the opening
- Insert spike from a standard cystoscopy administration infusion set into the left port with a twisting motion
- Infusion line should be clamped until the start of infusion
- Place bag of solution inside appropriately sized pressure cuff and inflate cuff to apply sufficient pressure for expression of fluid
- Prior to infusion, the solution container should be suspended from a sufficient height to allow for a steady stream of solution
- Servator C SALF should be administered immediately upon procurement of the donor heart
- Flushing should be continued until the heart is uniformly pale and the effluent is relatively clear
- Discard any unused product immediately after use

The suggested starting volume for adult transplants is 1 to 2 liters for in situ aortic flush. The flush volume may be incrementally increased at the discretion of the surgeon. The safety and efficacy of Servator C SALF in preserving hearts procured from pediatric donors or hearts transplanted to pediatric patients have not been studied.

Additional solution should be dispensed into the containers holding the heart. Seal the container aseptically. The organ storage container should be maintained within a well insulated transport container. Ice should be used to surround the organ storage container, but should not be used within the container where the ice could come in direct contact with the heart.

HOW SUPPLIED

Code = SERVC10DMA

- 1,000 mL Servator C SALF Cold Storage Solution in 1 liter bags
- Shelf carton of 10
- Store product at refrigerated temperatures 2˚- 8˚C (36˚- 46˚F) until use
- Avoid excessive heat
- Do not freeze
- Do not use if discolored or if particulates are present
- Do not use after the expiration date on the solution bag
- For single use only
- Materials Required For Use (Not Provided)

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Date of revision: October 2020

JFISERC10A NO-6516A3 r1 Tes