Instructions to use
LACTOCITRATE®

1. Purpose

Lactocitrate is a dialysis fluid designed for continuous venovenous haemodialysis (CVVHD) with regional citrate anticoagulation (RCA). It is administered preferrably with 4% trisodium citrate (4%TSC) and parallel substitution of calcium ($CaCl_2$). Lactocitrate may be used only on devices for continuous renal replacement therapy (CRRT) which, besides blood, dialysis and filtration pumps should have also integrated pumps for citrate and calcium infusion.

2. Content

Lactocitrate is supplied as a single chamber bag in total volume of 5000ml.

Dialysis fluid ready for use contains:

Sodium lactate	2.017 g/l
Glucose	1.001 g/l
Sodium chloride	6.550 g/l
Potassium chloride	0.075 g/l
Magnesium chloride hexahydrate	0.305 g/l
Potassium dihydrogenphosphate	0.136 g/l

Others: Water for injection

Concentration of ion and glucose are as follows:

Na^+	130	mmol/l
K^+	2.0	mmol/l
Mg^{2+}	1.5	mmol/l
P^-	1.0	mmol/l
Cl^-	116	mmol/l
$Lactate^-$	18	mmol/l
Glucose	5.6	mmol/l
pH	5.6	
Osmolality	274	mosmol/l

3. Way of application

User should become familiar with RCA and instructed by producer before using Lactocitrate. 4%TSC must be given in predilution. A proportion of 4%TSC to blood flow should be about 1:34, which is made of infusion of 4 mmol of citrate per liter of blood. The dosage of 4%TSC is guided by postfilter Ca^{2+} concentration, which should decrease below 0.4 mmol/l. Regular controls of postfilter Ca^{2+} are mandatory, preferrably every 3-4 hours. A calcium solution (concentration range 50-500 mmol/l) must be given by systemic infusion either to separate central venous line or into the distal venous blood set before connection to dialysis catheter. A suggested starting dose is 1.7 mmol Ca^{2+} per liter of applied dialysis fluid, i.e. 2 L/h of Lactocitrate requires approximately 3.4 mmol/h of calcium. The calcium dosage is guided by systemic arterial Ca^{2+}, which should remain between 0.9 and 1.3 mmol/l. Regular controls every 6h are advised.
The acid-base balance of a patient may be changed by proportion of 4%TSC infusion in relation to blood flow (alkalising) to citrate removal by dialysis flow (acidifying). Thus in case of metabolic alkalosis the increase of dialysis flow corrects the pH and BE towards normal. A balanced acid-base status is typically reached with the dosage of 1.5-3.0 L/h of Lactocitrate and a blood flow of 100-150 ml/min. These flows were tested with filters of sufficient areas not limiting transfer of solutes. Lactocitrate has a higher level of magnesium compensating its losses during RCA and normal level of phosphorus limiting hypophosphataemia during CRRT.

4. Dosage in continuous haemodialysis

If not indicated otherwise the expected efficiency of haemodialysis treatment is reached with dosage of 1.5 to 2.5 L/h of dialysis fluid in adults, i.e. 20-25 ml/kg.h. Adequate blood flow is between 90-100 ml/min and 100-120 ml/min for patients above 100 kg of body weight. In case of higher blood flows up to 150 ml/min and related higher dosage of 4%TSC the requirement is for 2.0-3.0 L/h of dialysis fluid. The fluid has not been tested in children yet.

5. Contraindications

Contraindication to Lactocitrate is other than citrate (RCA) anticoagulation of CRRT. Intolerance of citrate, its body cummulation and increase of calcium index (see notes below, intolerance of citrate is not related to Lactocitrate) do not allow for continuation of RCA with Lactocitrate.
Lactocitrate contains lactate buffer which is readily metabolised in the intermediate metabolism. Primary hyperlactataemia implicating, for example, an imbalance between systemic oxygen dosage and consumption or liver failure are relative contraindications to Lactocitrate. Thus another fluid might be used, e.g. with bicarbonate buffer.

6. Side effects

Lactocitrate does not posses side effects when correctly administered however, its higher dosage above 2.5 L/h may increase plasmatic lactate concentration which is typically at the upper limit of normal (median 1.5-2.0 mmol/l). This mild hyperlactataemia made by input of exogennous lactate does not negatively influence organ functions, morbidity or mortality.

7. Precautions

- Do not use as intravenous fluid
- Use only clear fluid
- Control bag for damage, leaks and intact connectors with safety locks
- Fluid must not be used if wrapping or safety lock is broken
- Discard not used remaining fluid

8. Connection to extracorporeal circuit

Bag with dialysis fluid is connected to dialysis circuit according to instructions for a CRRT device. Any contaminations of dialysis fluid and parts of the circuit in contact with the fluid must be prevented.
Bag with Lactocitrate which is disconnected from dialysis circuit should be discarded.
Lactocitrate must not be given intravenously nor may be given by infusion into the blood circuit of CRRT device.
Before use the Lactocitrate should be warmed up by a CRRT device to the body level to avoid decrease of patient´s temperature during therapy.

Notes

Dialysis fluid for citrate CVVHD in a single chamber bag.

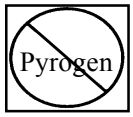
- **Dialysis fluid must be used only with citrate in predilution (regional citrate anticoagulation)**
- **Dialysis fluid without calcium: separate calcium infusion is mandatory**
- **Fluid contains increased magnesium concentration compensating loss of magnesium during citrate anticoagulation.**
- **Fluid contains normal phosphorus level preventing hypophosphataemia during CRRT**
- **The setting of citrate CVVHD must be thoroughly checked before start of therapy. Particularly important is the avoidance of incorrect connection of citrate and calcium infusions.**
  Correct setting should be confirmed by measurement of citrate induced decrease of ionised calcium concentration in the extracorporeal circuit 20 to 30 min after start of therapy at the latest. If this is not taking place the setting must be checked for incorrect connection of citrate and calcium potentially leading to patient´s harm.
- Use high-flux dialysis filter with minimum active surface of 1.4 m^2 and change filter with circuit at least after every 72 h.
- Reduced metabolism of citrate may lead to acidosis, hypocalcaemia or increased requirement for calcium substitution, e.g. in patients with liver dysfunction. The calcium index (total to ionised Ca) should be controlled every 12h in systemic arterial blood. Ca^{tot}/Ca^{2+} must be under 2.5. Ceasing of RCA and a change for another anticoagulation modality is advised in case of its increase and cummulation of citrate in the body.
- Steam sterilised.
- **Store in temperature between 4°C and 25 °C**
- **Date of expiration: see leaflet**
- **Single use only**

9. Information on bag liquidation

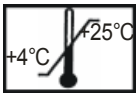
Potentially toxic waste

Symbols on cover:

Read instructions for use



Nonpyrogennous fluid



Store at +4 to +25°C

Single use

Steam sterilised

Certified

Manufacturer: Biomedica, spol. s r.o., Pekařská 8, 155 00 Praha 5, Česká republika
Date of issue: 03.03.2014