

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Regiocit Solution for haemofiltration

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:

Sodium chloride 5.03 g/l

Sodium citrate 5.29 g/l

Sodium, Na⁺ 140 mmol/l

Chloride, Cl⁻ 86 mmol/l

Citrate, C₆H₅O₇³⁻ 18 mmol/l

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for haemofiltration

The solution is sterile, clear and colourless and free from bacterial endotoxins.

Theoretical osmolarity: 244 mOsm/l

pH ≈ 7.4

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Regiocit is indicated as replacement fluid for continuous renal replacement therapy (CRRT) using regional citrate anticoagulation. Citrate is particularly relevant when systemic anticoagulation with heparin is contraindicated, for example in patients with increased bleeding risks.

In paediatric patients, Regiocit is indicated in all age groups provided that the equipment used is adapted to the weight of the child.

4.2 Posology and method of administration

Posology

The pre-filter infusion rate of Regiocit must be prescribed and adapted relative to the blood flow rate. The prescription of Regiocit must consider the flow rates of the effluent and other therapeutic fluids, the patient's fluid removal requirements, additional fluid inputs and outputs, and the desired acid-base and electrolyte balance.

Flow rate for anticoagulation of the extracorporeal circuit should be titrated to achieve a post-filter concentration of ionized calcium in the range 0.25 to 0.35 mmol/l. The patient's systemic ionized calcium concentration should be maintained in the normal physiologic range by adjustment of calcium supplementation.

Flow rates for Regiocit in adult and adolescents:

- In continuous veno-venous haemofiltration
 - 1-2.5 l/h with a blood flow rate between 100 and 200 ml/min.
- In continuous veno-venous haemodiafiltration
 - 1-2 l/h with a blood flow rate between 100 and 200 ml/min.

Paediatric population:

For neonates to toddlers (0 to 23 months) Regiocit should target a dose of 3 mmol citrate per litre of blood flow in continuous veno-venous haemofiltration or haemodiafiltration. For children (2 to 11 years) dosage should be adapted to both the weight of the patient and the blood flow rate.

Special populations:

In the elderly population there is no specific modification of the dosage compared to adults.

Hepatic impairment or shock:

In case of liver failure (including e.g. liver cirrhosis or acute liver failure) or shock, initial starting dose of citrate should be reduced as metabolism may be inadequate. (see section 4.3 and 4.4).

Method of administration

For intravenous use. Regiocit must be used with a dialysis machine intended for CRRT in pre-dilution mode only, using a dedicated pump for citrate anticoagulation where the solution flow rate is automatically adapted based on an operator set target dose (mmol citrate/l blood).

Regiocit should be used only by, or under the direction of, a physician competent in the application of regional citrate anticoagulation in CRRT.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

Severely impaired liver function

Shock with muscle hypoperfusion

4.4 Special warnings and precautions for use

Regiocit is not for direct intravenous infusion. It should be used in predilution only, with a dialysis machine for CRRT. The dialysis machine must be suitable for citrate anticoagulation.

Use only if the overwrap and solution bag are undamaged. Use of a contaminated solution may cause sepsis and shock.

Considering the composition of Regiocit, other solutions used in the treatment must have appropriate hydrogen carbonate concentration.

The patient's haemodynamic status, fluid balance, glucose level, electrolyte and acid/base balance should be closely monitored before and during treatment.

Regiocit does not contain potassium, calcium, magnesium, phosphate or glucose. Blood concentration and patients' needs should be assessed several times daily including assessment of infusate inputs and all outputs in order to provide supplementation when needed (see sections 4.8 and 4.9).

As citrate chelates calcium and magnesium which are thus eliminated with the effluent, this could cause hypocalcaemia (see sections 4.8 and 4.9) and/or hypomagnesaemia (see section 4.8). Infusion of calcium for compensation of losses is standard practice and supplementation with magnesium might as well be necessary.

Accumulation of citrate due to metabolic failure:

Special attention is required in patients with liver failure (including e.g. liver cirrhosis or acute liver failure) or shock (see section 4.2 and 4.3), metabolism of citrate may be markedly reduced and patients exposed to accumulation of citrate. If haemofiltration with citrate is applied in these patients, more frequent monitoring of citrate accumulation is advised. If the liver and skeletal muscles fail to metabolise citrate, hydrogen carbonate is not produced and citrate can accumulate. Metabolic acidosis and ionized hypocalcaemia ensue. Accumulation of citrate can be detected by monitoring ionized calcium, total calcium and hydrogen carbonate concentration in the blood. If citrate accumulates, the ratio of total to ionized calcium in the blood rises. If the total/ionized calcium ratio rises above 2.3, the citrate buffer should be reduced or stopped. To correct for metabolic acidosis, hydrogen carbonate has to be replaced. CRRT can be continued without anticoagulation or other means of anticoagulation have to be considered.

Accumulation of citrate due to inappropriate infusion:

Inappropriate infusion of too large amounts of citrate (see also section 4.9) causes acute hypocalcaemia and metabolic alkalosis and may expose patient to neurologic and cardiac complications. Treatment consists of discontinuation of the citrate infusion and the infusion of calcium.

Systemic hypocalcaemia (low ionized calcium) may be the result of two different mechanisms:

- Insufficient compensation of calcium loss with citrate through the filter (low ionized calcium and low total calcium) which requires adjusting the flow rate of calcium solution for supplementation ;
- Accumulation of citrate as a result of poor metabolism in the liver and muscles (high total calcium/ionized calcium ratio) which requires partial or complete switch from Regiocit to a replacement solution without citrate (continuous venovenous haemofiltration) or combined reduction or stopping of Regiocit flow rate and increase of the dialysate flow rate to increase the removal of citrate (continuous venovenous haemodiafiltration).

Systemic hypercalcaemia

High total calcium with high ionized calcium may happen due to excessive perfusion of the calcium replacement solution. It requires reduction in the calcium solution flow rate.

High total calcium with high total calcium to ionized calcium ratio maybe the result of calcium citrate accumulation in relation to excessive flow rate of citrate or inability to metabolize a sufficient amount of citrate. It should lead to reduction or discontinuation of citrate infusion.

Metabolic acidosis

Citrate may accumulate if the liver and skeletal muscles fail to provide adequate metabolism of citric acid which can occur in liver cirrhosis or acute liver failure. In these cases, citric acid accumulates and metabolic acidosis results. In these patients, the classical anion gap rises as well, reflecting the increase in ionized citrate. In most circumstances, lactate also accumulates.

Metabolic acidosis as a result of a failure to metabolize citric acid can be diagnosed early by routine metabolic monitoring and corrected by discontinuation of citrate infusion and adjustment of replacement fluid composition.

Metabolic alkalosis

Some patients require and tolerate high citrate infusion rates to maintain ionized calcium levels in the extracorporeal circuit within the desired range. Citrate generates hydrogen carbonate and therapy can result in or contribute to metabolic alkalosis.

This can be managed by reducing blood flow rate, thus allowing for a decrease in the citrate infusion rate into the patient. Metabolic alkalosis may also be managed by increasing dialysate flow rate which also maintains CRRT dose and by infusing 0.9 % sodium chloride post-filter. Accumulation of citrate with metabolic alkalosis and hypocalcaemia may also occur if the patient has received a large volume of citrate containing blood products and CRRT dose is too low.

The instructions for use must be strictly followed. Incorrect use of the access ports or other restrictions to fluid flow might lead to incorrect patient weight loss and may result in machine alarms. Continuing treatment without resolving the originating cause may result in patient injury or death.

Regiocit is for single use only. Any unused solution must be discarded.

Use only if the solution is clear and free from visible particles.

CRRT results in sodium removal proportional to plasma water sodium content. To avoid a drop in the blood sodium level in the patient (hyponatraemia) sodium losses must be balanced as part of overall fluid and electrolyte management (see section 4.8). Administration of both CRRT related dialysis fluids and those outside of the CRRT prescription require careful assessment.

4.5 Interaction with other medicinal products and other forms of interaction

The blood concentration of filterable drugs may be reduced during treatment. Corresponding corrective therapy should be instituted if necessary.

No pharmacodynamic drug interactions among the constituents of Regiocit are expected. Interactions could only be expected by inadequate or incorrect therapeutic use of the solution (see sections 4.4 and 4.9).

It is the responsibility of the physician to determine the compatibility of an additive medication with this medicine by checking for possible colour change and/or possible precipitation. Before adding a medication, verify if it is soluble and stable in this medicine.

However, the following interactions are conceivable with medicinal products containing:

- Calcium, which may reduce the anticoagulation effect and /or
- Sodium hydrogen carbonate, which may increase the risk of a high concentration of hydrogen carbonate in the blood (metabolic alkalosis – see section 4.8).

4.6 Fertility, pregnancy and lactation

Fertility:

No effects on fertility are anticipated, since sodium, chloride and citrate are normal constituents of the body.

Pregnancy and lactation:

There are no documented clinical data on the use of Regiocit during pregnancy and lactation. Regiocit should only be administered to pregnant and lactating women if clearly needed.

4.7 Effects on ability to drive and use machines

Regiocit is not known to affect your ability to drive or use machines.

4.8 Undesirable effects

Undesirable effects can result from the Regiocit solution or the dialysis treatment. Special precautions for use have been described in section 4.4.

The following undesirable effects have been described in published literature (Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/100$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data):

Metabolism and nutrition disorders	
Common	Electrolyte imbalances, e.g hypomagnesaemia (see section 4.4), hypocalcaemia (see section 4.4 and 4.9), hypercalcaemia (see section 4.4), hyponatraemia (see section 4.4)
	Disturbances in acid-base balance including metabolic acidosis (see section 4.4 and 4.9) and metabolic alkalosis (see section 4.4, 4.5 and 4.9)
Not known	Fluid retention
	Fluid imbalance, e.g. dehydration (see section 4.4)
Vascular disorder	
Not known	Hypotension*
Gastrointestinal disorder	
Not known	Nausea*
	Vomiting*

Musculoskeletal and connective tissue disorders	
Not known	Muscle spasms*

* undesirable effects related to the dialysis treatment

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product 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 listed in Appendix V.

4.9 Overdose

Undesirable administration of too high volumes of replacement solution may lead to an overdose, which can cause a life threatening situation for the patient. This may result in pulmonary oedema and congestive heart failure in relation with fluid overload and in hypocalcaemia (see section 4.4) and metabolic alkalosis (see section 4.4) due to citrate overload in relation to the blood flow. This derangement needs to be corrected immediately by stopping/lowering the amount of replacement solution and by the intravenous administration of calcium.

In patients with poor citrate metabolism (liver failure or shock) citrate may accumulate.

Metabolic acidosis (see section 4.4) and ionized hypocalcaemia (see section 4.4 and 4.8) may ensue.

Regiocit should thus be either reduced or stopped.

To correct for metabolic acidosis, hydrogen carbonate has to be replaced. Continuous renal replacement therapy can be continued without anticoagulation or other means of anticoagulation have to be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Haemofiltrates

ATC code: B05ZB

Citrate provides anticoagulation by its ability to form complexes with ionized calcium, making it unavailable to the clotting cascade. In Regiocit, sodium concentration has been set to 140 mmol/l as critically ill patients are prone to develop severe hyponatraemia. Chloride is set to the level required to balance cations as the solution is hydrogen carbonate free. Sodium and chloride are normal constituents of the human body and are considered to be pharmacologically inactive. Citrate is a normal metabolite in the human body that acts as a first intermediate substance in the Krebs cycle. Regiocit is deprived of potassium and glucose. Toxic effects due the use of Regiocit are not expected at therapeutic dose.

5.2 Pharmacokinetic properties

Citrate is a normal metabolite in the human body and an intermediate substance in the Krebs cycle. This physiological pathway is capable of processing high amounts of citric acid as long as it occurs at low concentrations. The Krebs cycle takes place in the mitochondria, and all cells that contain these cellular organelles can metabolize citrate. Tissues rich in mitochondria such as liver, skeletal muscles, and kidney therefore have a higher capacity for citrate generation and elimination.

Absorption and Distribution

Absorption and distribution of sodium and chlorides is determined by the patient's clinical condition, metabolic status, and residual renal function. Extracellular citrate can be transported from the blood across the plasma membrane by a group of proteins i.e. the plasma membrane citrate transporters (PMCTs) into the cells and then metabolized in various organs and tissues.

Biotransformation

In humans, citrate is an intermediate in the central metabolic pathway called Krebs cycle as mentioned above. Citrate is rapidly metabolized mainly in the liver, but can also be metabolized by other organs/tissues.

Elimination

Any excess of circulating citrate is normally excreted via the kidneys.

5.3 Preclinical safety data

There are no preclinical data considered relevant to clinical safety beyond data included in other sections of the SmPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

Dilute hydrochloric acid (for pH adjustment) E 507

6.2 Incompatibilities

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

6.3 Shelf life

18 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

Do not freeze.

6.5 Nature and contents of container

The container is a one-compartment bag made of a multilayer film containing polyolefins and elastomers. The bag is fitted with an injection connector (or spike connector) and a luer connector for the connection with a suitable haemofiltration solution line or pre-blood pump line. The bag contains 5000 ml solution and is overwrapped with a transparent overwrap made of polymer film. Each box contains two bags and one package leaflet.

Pack size: 2 x 5000 ml in a box

6.6 Special precautions for disposal and other handling

The solution can be disposed of via wastewater without harming the environment.

If a valve is located in the luer connector the following instructions for use shall be followed:

Remove the overwrap from the bag immediately before use. Aseptic technique should be used throughout administration to the patient. The solution should be used immediately after opening to avoid microbiological contamination.

I. If the luer connector is used, remove the cap with a twist and pull motion. Connect the male luer lock on the pre-blood pump line to the female luer connector on the bag using a push and twist motion. Ensure that the connection is fully seated and tighten. The connector is now open. Verify that the fluid is flowing freely. When the pre-blood pump line is disconnected from the luer connector, the connector will close and the flow of the solution will stop. The luer is a needle-less and swabbable port.

II. If the injection connector (or spike connector) is used, remove the snap-off cap. Introduce the spike through the rubber septum. Verify that the fluid is flowing freely.

If a frangible pin is located in the luer connector the following instructions for use shall be followed:

Remove the overwrap from the bag immediately before use. Aseptic technique should be used throughout administration to the patient. The solution should be used immediately after opening to avoid microbiological contamination.

I. If the luer connector is used, remove the cap and connect the male luer lock on the pre-blood pump line to the female luer connector on the bag, tighten. Using both hands, break the blue frangible pin at its base, and move it back and forth. Do not use a tool. Verify that the pin is completely separated and that the fluid is flowing freely. The pin will remain in the luer port during the treatment.

II. If the injection connector (or spike connector) is used, remove the snap-off cap. Introduce the spike through the rubber septum. Verify that the fluid is flowing freely.

7. MARKETING AUTHORISATION HOLDER

Gambro Lundia AB
Magistratsvägen 16
226 43 Lund
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation: {DD month YYYY}>

<Date of latest renewal: {DD month YYYY}>

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>