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, $C_6H_5O_7^{3-}$ 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 rate at which Regiocit is administered depends on the targeted citrate dose and the prescribed blood flow rate (BFR). 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. Regiocit should be prescribed and administration (dose, infusion rate, and cumulative volume) should be established only by a physician experienced in critical care medicine and CRRT.

The pre-filter infusion rate of Regiocit must be prescribed and adapted relative to the blood flow rate to achieve target blood citrate concentration of 3 to 4 mmol/l of blood.

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.

Citrate also acts as a buffer source (due to conversion to bicarbonate); the infusion rate of Regiocit must be considered in relation to the rate at which buffer administration occurs from other sources (e.g., dialysate and/or replacement fluid). Regiocit must be used together with a dialysis solution/replacement solution with appropriate bicarbonate concentration.

A separate infusion of calcium is always required. Adjust or stop calcium infusion according to physician's prescription when anticoagulation is stopped.

Monitoring of the post-filter blood ionized calcium (iCa), systemic blood iCa, and total blood calcium levels in conjunction with other laboratory and clinical parameters are essential to guide appropriate Regiocit dosage based on the desired level of anticoagulation (see Section 4.4).

Plasma levels of sodium, magnesium, potassium, and phosphate should be monitored regularly and should be supplemented as needed.

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:

Dose reduction may be needed in patients with mild to moderate hepatic impairment (e.g., Child-Pugh ≤12). In case of liver impairment (including e.g. liver cirrhosis), initial starting dose of citrate should be reduced as metabolism may be inadequate (see section 4.4). Frequent monitoring of citrate accumulation is advised. Regiocit must not be administered to patients with severely reduced liver function or shock with muscle hypoperfusion (e.g., conditions such as septic shock and lactic acidosis) due to limited citrate metabolism (see section 4.3).

Method of administration

For intravenous use. Regiocit must be used with appropriate extracorporeal renal replacement equipment 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 appropriate extracorporeal renal replacement equipment intended for CRRT. The dialysis machine must be suitable for citrate anticoagulation.

Regiocit may be warmed to 37°C to enhance patient comfort. Warming of the solution prior to use should be done with dry heat only. Solutions should not be heated in water or in a microwave oven due to the potential for patient injury or discomfort. Regiocitshould be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer unless the solution is clear and the seal is intact.

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.

Regiocit contains citrate, which can influence the patient's electrolyte and acid–base balance.The patient's haemodynamic status, fluid balance, glucose level, electrolyte and acid/base balance should be closely monitored before and during treatment.

Closely monitor sodium, magnesium, potassium, phosphate, and calcium. Blood concentration and patients' needs should be assessed several times daily including assessment of infusate inputs and all outputs. Infusion of electrolytes may be needed to supplement any loss (see sections 4.8 and 4.9).

Regiocit contains no calcium, and may lead to systemic ionized hypocalcaemia due to loss of calcium bound to citrate in the effluent and/or in the case of systemic citrate accumulation.

Regiocit contains no magnesium. Use of Regiocit may result in hypomagnesaemia due to CRRT effluent losses. Patient should be monitored as infusion of magnesium may be necessary.

Regiocit contains no glucose. Administration of Regiocit may lead to hypoglycaemia. Blood glucose levels should be monitored regularly.

Regiocit contains no potassium. The serum potassium concentration must be monitored before and during CRRT.

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. If citrate accumulation develops and/or metabolic acidosis develops or worsens during therapy with Regiocit, the infusion rate may need to be decreased or its administration stopped.

Metabolic alkalosis
Some patients require and tolerate high citrate infusion rates to maintain ionized calcium levels in the extracorporeal circuit within the desired range. Regiocit contains citrate, which contributes to the overall buffer load. Additional sodium hydrogen carbonate (or buffer source) contained in the CRRT fluids or in other fluids administered during therapy may increase the risk of metabolic alkalosis. Metabolic alkalosis may occur if the net citrate administration rate exceeds that which is necessary to maintain acid–base balance (see section 4.2).

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, or change the composition of the CRRT solution. 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.

Blood calcium levels should be monitored regularly in patients with metabolic alkalosis since this condition may potentiate hypocalcaemia.

Use in Patients with Hepatic Impairment
Metabolism of citrate (to bicarbonate) may be impaired in patients with hepatic impairment, resulting in accumulation of citrate. If Regiocit is administered to patients with mild to moderate hepatic impairment (e.g., Child-Pugh ≤12), frequent monitoring of pH, electrolytes, total-to-ionized calcium ratio, and systemic ionized calcium is important to avoid electrolyte and/or acid–base imbalance (see Section 4.2). Regiocit should not be used in patients with severe hepatic impairment (see Section 4.3).

Hemodynamic Status and Fluid Balance
The patient's hemodynamic status and fluid balance should be monitored throughout the procedure.
- In case of hypervolaemia, the net ultrafiltration rate prescribed for the CRRT device can be increased, and/or the rate of administration of solutions other than replacement fluid and/or dialysate can be reduced.
- In case of hypovolaemia, the net ultrafiltration rate prescribed for the CRRT device can be reduced, and/or the rate of administration of solutions other than replacement fluid and/or dialysate can be increased.

Hypoosmolarity/Hypotonicity
Regiocit is hypoosmolar/hypotonic relative to standard CRRT replacement fluids and should be used with caution in patients with traumatic brain injury, cerebral oedema, or increased intracranial pressure.

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.

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/dialysable drugs may be reduced during treatment due to their removal by the extracorporeal filter. Corresponding corrective therapy should be instituted if necessary to establish the desired blood concentrations for drugs removed during treatment.

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).

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

- vitamin D and other vitamin D analogues, as well as medicinal products containing calcium (e.g., calcium chloride or calcium gluconate used for maintenance of calcium homeostasis in CRRT patients receiving citrate anticoagulation) can increase the risk of hypercalcaemia, and can result in a reduced anticoagulation effect.

- 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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥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), hypokalaemia (see section 4.4), hypophosphataemia (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 to report any suspected adverse reactions via:
HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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 the amount of replacement solution and by the intravenous administration of calcium. Careful calcium supplementation can reverse the effects of an overdose. The risk can be minimised by close monitoring during treatment.

In patients with impaired citrate metabolism (liver failure or shock), overdose may be manifested as citrate accumulation, metabolic acidosis (see section 4.4), systemic total hypercalcaemia (see section 4.4) and ionized hypocalcaemia (see section 4.4 and 4.8) along with increased total calcium/ionized calcium ratio.

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. Regiocitis 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 acidas 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.

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.

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.

The following instructions for use shall be followed:

Aseptic technique should be used throughout the handling and administration to the patient. Remove the overwrap from the bag immediately before use. Use only if the overwrap is not damaged, all seals are intact, and the solution is clear. Press bag firmly to test for any leakage. If leakage is discovered, discard the solution immediately since sterility can no longer be assured. 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. The injection port is a swabbable port. Introduce the spike through the rubber septum. Verify that the fluid is flowing freely.
Before adding a substance or medication, verify that it is soluble and stable in Regiocit, and that the pH range of the product is appropriate. Additives known or determined to be incompatible should not be added.

The instructions for use of the medication to be added and other relevant literature must be consulted.
After addition, if there is a discoloration and/or the appearance of precipitates, insoluble complexes, or crystals, do not use.
Mix the solution thoroughly when additives have been introduced. The introduction and mixing of additives must always be performed prior to connecting the solution bag to the extracorporeal circuit.
The solution is for single use only. Discard any unused portion.

7 MARKETING AUTHORISATION HOLDER

Baxter Holding B.V.
Kobaltweg 49
3542CE Utrecht
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA2299/054/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th November 2014
Date of last renewal: 1st October 2019

10 DATE OF REVISION OF THE TEXT

February 2024