Package leaflet: Information for the user

Regiocit Solution for haemofiltration
Citrate, Sodium, Chloride

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What this medicine is and what it is used for
2. What you need to know before you use this medicine
3. How to use this medicine
4. Possible side effects
5. How to store this medicine
6. Contents of the pack and other information

1. What this medicine is and what it is used for

This medicine is a solution for haemofiltration and prevents blood clotting during continuous renal replacement therapy (CRRT), which is a form of dialysis treatment. This medicine is used for critically ill patients, particularly when the normal medicine used to prevent blood clotting (heparin) is inappropriate. Citrate provides anticoagulation by binding to calcium in the blood.

2. What you need to know before you use this medicine

Do not use this medicine in case of:
Allergy to the active substances or to any of the other ingredients (listed in section 6)
Severely impaired liver function
Severely decreased blood flow in the muscles

Warning and precautions

Talk to your doctor, pharmacist or nurse before using this medicine.

This medicine is not for direct intravenous infusion. It should be used only with a machine capable of performing continuous renal replacement therapy (CRRT), which is a type of dialysis specifically for critically ill patients with kidney failure. The CRRT 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. Regiocit should be inspected visually for particulate matter and discoloration prior to administration. Do not administer unless the solution is clear, free from visible particles and the seal is intact.

If the overwrap or solution bag is damaged, the solution may become contaminated and must not be used.

Besides this medicine, the treatment involves other fluids that are infused. The composition or rate of administration of these other fluids may need to be adjusted to be compatible with this medicine.
Your doctor will closely monitor your haemodynamic status, fluid balance, glucose level, electrolyte and acid/base balance before and during treatment. Sodium, magnesium, potassium, phosphate and calcium will be closely monitored.

Adjustments to the therapy will be made if needed.

Regiocit contains no calcium. Use of Regiocit may lead to low calcium levels in the blood (hypocalcaemia).

Regiocit contains no magnesium. Use of Regiocit may result in low magnesium in the blood (hypomagnesaemia). Magnesium blood level will be closely monitored and infusion of magnesium may be necessary.

Regiocit contains no glucose. Administration of Regiocit may lead to low glucose in the blood (hypoglycaemia). Blood glucose levels should be monitored regularly.

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

Your doctor will pay special attention to the citrate infusion rate. Too much citrate causes low blood levels of calcium and high blood pH, which may lead to neurologic and cardiac complications. High blood pH can be corrected by adjusting dialysis settings and by infusing 0.9 % sodium chloride solution post-filter or change the composition of the CRRT solution. Low blood levels of calcium can be treated by infusion of calcium.

Special attention is required by your doctor if you suffer from liver failure or shock. The metabolism of citrate may be markedly reduced resulting in accumulation of citrate accompanied by low blood pH. Your doctor will decide if your treatment has to be adjusted. If the total/ionized calcium ratio rises above 2.3, the citrate buffer should be reduced or stopped.

If Regiocit is administered to patients with hepatic impairment, frequent monitoring of pH, electrolytes, total-to-ionized calcium ratio, and systemic ionized calcium is important to avoid electrolyte and/or acid–base imbalance. Do not use if you have a severe hepatic impairment.

In case of abnormally high volume of fluid in the body (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 abnormally low volume of fluid in the body (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.

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.

Other medicines and Regiocit
Tell your doctor, pharmacist or nurse if you are taking, or have recently taken, any other medicines, including medicines obtained without a prescription. This is because the concentration of other medicines may be reduced during dialysis treatment. Your doctor will decide if any changes in the dosage of your medicines should be made.
In particular, tell your doctor if you are using medicinal product containing any of the following:

- Vitamin D and other medicinal products containing calcium and medicinal products containing calcium chloride or calcium gluconate; as they can increase the risk of a high concentration of calcium in the blood *(hypercalcaemia)* and can result in a reduced anticoagulation effect.
- Sodium hydrogen carbonate; as they may increase the hydrogen carbonate level in your blood.

Pregnancy, breast-feeding and fertility
Fertility:
No effects on fertility are anticipated, since sodium, chloride and citrate are normal constituents of the body.

Pregnancy and breast-feeding:
There are no documented clinical data on the use of this medicine during pregnancy and breast-feeding. This medicine should only be administered to pregnant and breast-feeding women if clearly needed.

Driving and using machines
This medicine is not known to affect your ability to drive or use machines.

3. How to use this medicine

For intravenous use. This medicine is to be used in hospitals and administered by medical professionals only. The volume used, and therefore the dose of this medicine, will depend on your condition. The dose volume will be determined by your doctor.

The recommended flow rates for this medicine in adults 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.

Use in older people:
The recommended flow rates are the same as for adults and adolescents.

Use in children:
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.

Liver failure or shock:
In these conditions, the initial starting dose of citrate should be reduced.

Instructions for use
Regiocit will be given to you in a hospital. Your doctor will know how to use Regiocit.
For instructions for use see the end of this leaflet.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Your blood will be regularly controlled by a doctor or nurse in order to find possible side effects. Use of this solution could cause:

Common: may affect up to 1 in 10 people
• Acid/base imbalance in the blood
• Imbalances in the level of electrolytes in the blood (e.g. drop in the calcium, sodium, magnesium, potassium and/or phosphate level in the blood or increase in the calcium level in the blood)

Not known: frequency cannot be estimated from the available data
• Imbalance in the level of fluid in the body (dehydration, retention of fluid in the body)
• • Decreased blood pressure *
• Feeling sick*, vomiting*
• Cramps *

* Side effects related to the dialysis treatment rather than this medicine.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.
You can also report side effects directly via
United Kingdom:
Via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

Republic of Ireland:
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.

Malta:
ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store this medicine

Keep this medicine out of the sight and reach of children.

This medicinal product does not require any special storage conditions.
Do not freeze.

Do not use this medicine after the expiry date which is stated on the label and the packaging. The expiry date refers to the last day of that month.

Do not use this medicine if you notice damage to the product or visible particles in the solution.

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

6. Contents of the pack and other information

What this medicine contains
Composition:

Sodium chloride	5.03 g/l
Sodium citrate	5.29 g/l

The active substances are:

Sodium, Na^+	140 mmol/l
Chloride, Cl^-	86 mmol/l
Citrate, $C_6H_5O_7^{3-}$	18 mmol/l

Theoretical osmolarity: 244 mOsm/l
pH ≈ 7.4

The other ingredients are:
Dilute hydrochloric acid (for pH adjustment) E507
Water for injections

What this medicine looks like and contents of the pack
This medicine is a clear and colourless solution for haemofiltration packed in a one-compartment bag made of a multilayer film containing polyolefins and elastomers. The solution is sterile and free from bacterial endotoxins. Each bag contains 5000 ml solution and the bag is overwrapped with a transparent film. Each box contains two bags and one package leaflet.

Marketing Authorisation Holder
Republic of Ireland and Malta:
Baxter Holding B.V.
Kobaltweg 49
3542 CE Utrecht
Netherlands

United Kingdom:
Baxter Healthcare Ltd,

Caxton Way, Thetford,
Norfolk, IP24 3SE,
United Kingdom

Manufacturer
Bieffe Medital S.p.A.
Via Stelvio, 94
23035 Sondalo (SO)
Italy

Or

Baxter Healthcare S.A.
Moneen Road,
Castlebar
County Mayo
F23 XR63
Ireland

This medicine is authorised in the Member States of the European Economic Area and in the United Kingdom (Northern Ireland) under the following names: Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom (Northern Ireland): Regiocit
Bulgaria: Regiocit (Региоцит)

This leaflet was last revised in 03/2023

The following information is intended for healthcare professionals only:

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 a target blood citrate concentration of 3 to 4 mmol/l of blood. 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.

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 $\leq$12). In case of liver impairment (including e.g. liver cirrhosis), initial starting dose of citrate should be reduced as metabolism may be inadequate. 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

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 and metabolic alkalosis 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 minimized by close monitoring during treatment.

In patients with impaired citrate metabolism (liver failure or shock), overdose may be manifested as citrate accumulation, metabolic acidosis, systemic total hypercalcaemia and ionized hypocalcaemia 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.

Preparation and/or handling
The solution can be disposed of via wastewater without harming the environment.

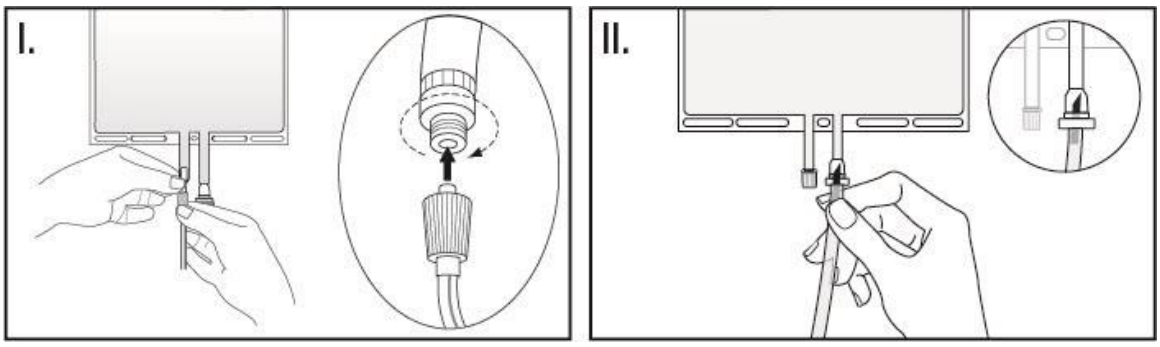
The following instructions for use shall be followed:

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. (See figure I. below)

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. (See figure II. below)



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.