Regiocit, Solution for haemofiltration

"百特"局部抗凝檸檬酸血液過濾用溶液

07-19-00-1287

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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 solution is indicated as replacement fluid before dialyzer 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** solution 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** solution is administered depends on the targeted citrate dose and the prescribed blood flow rate (BFR). The prescription of **Regiocit** solution 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** solution 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** solution 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.

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** solution must be considered in relation to the rate at which buffer administration occurs from other sources (e.g., dialysate and/or replacement fluid). **Regiocit** solution 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** solution 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** solution 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** solution 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** solution 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** solution 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 solution 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 solution 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 solution 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. **Regiocit** solution should 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** solution, other solutions used in the treatment must have appropriate hydrogen carbonate concentration.

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

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

Regiocit solution 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** solution to a replacement solution without citrate (continuous venovenous haemofiltration) or combined reduction or stopping of **Regiocit** solution 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** solution, 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** solution 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** solution 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** solution 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 solution 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** solution 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** solution during pregnancy and lactation. **Regiocit** solution should only be administered to pregnant and lactating women if clearly needed.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Regiocit solution 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

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 solution 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** solution, 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** solution is deprived of potassium and glucose. Toxic effects due the use of **Regiocit** solution 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

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

Store below 30 °C. 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

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. 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** solution, 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.

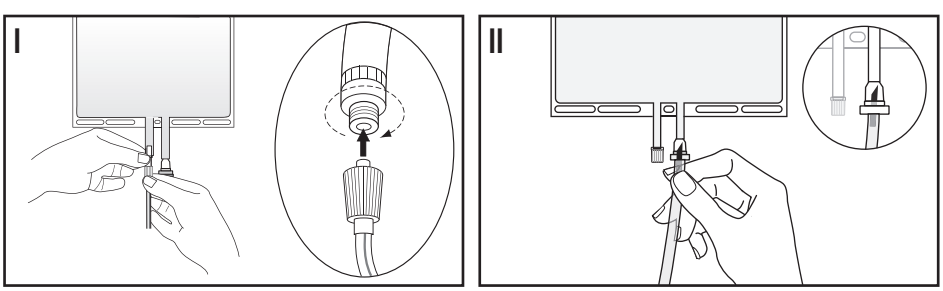
The solution is for single use only. Discard any unused portion.

7. NAME AND ADDRESS OF MANUFACTURER

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

8. DATE OF REVISION OF THE TEXT

MM/YYYY



" 百特 " 局部抗凝檸檬酸血液過濾用溶液

Regiocit, Solution for haemofiltration

衛部藥輸字第027649號

本藥限由醫師使用

1. 醫藥產品名稱

" 百特 " 局部抗凝檸檬酸血液過濾用溶液

Regiocit, Solution for haemofiltration

2. 定性與定量成分

成分：

氯化鈉	5.03 g/l
檸檬酸鈉	5.29 g/l
鈉 (Na^+)	140 mmol/l
氯 (Cl^-)	86 mmol/l
檸檬酸鹽 ($C_6H_5O_7^{3-}$)	18 mmol/l

如需賦形劑的完整清單，請參閱第 6.1 節。

3. 藥物劑型

血液過濾用溶液

溶液為無菌狀態，澄清無色，且無細菌內毒素。

理論滲透壓：244 mOsm/l

pH ≈ 7.4

4. 臨床特性

4.1 適應症

採用局部檸檬酸鹽抗凝 法(regional citrate anticoagulation) 來進行連續性腎功能替代治療 (CRRT) 時，可使用 Regiocit 溶液做為 過濾器前的 置換液。當採用肝素的全身性抗凝法屬於禁忌時，檸檬酸鹽就格外地重要 (例如在出血風險增加的病人身上)。

對於兒科病人來說，Regiocit 溶液適用於所有年齡層，但是所使用的設備應根據兒童體重做調整。

4.2 用量與用法

用量

Regiocit 溶液的輸注速率，取決於目標檸檬酸鹽劑量與處方的血液流速 (blood flow rate，BFR)。Regiocit 溶液的處方必須考量到廢液與其他治療液體的流速、病人的脫水量需求、額外的液體輸入與輸出，以及所需要的酸鹼與電解質平衡。Regiocit 溶液僅應由具有重症醫學及連續性腎臟替代療法 (CRRT) 經驗的醫師開立處方及施用 (劑量、輸注速率以及累積量)。

Regiocit 溶液的過濾前輸注速率，必須相對於血液流速開立處方和調整，以達到每公升血液 3 至 4 mmol 的目標血中檸檬酸鹽濃度。

進行體外循環迴路抗凝的流速應要逐步調整以達到過濾器後游離鈣離子(ionized calcium)濃度落在 0.25 至 0.35 mmol/l的範圍內。病人的全身性游離鈣離子濃度應以調整靜脈鈣補充的方式，維持在正常生理範圍內。

檸檬酸鹽也是一種緩衝來源 (因為可轉換成碳酸氫鹽)；設定 Regiocit 溶液的輸注速率時，必須考量到其他來源之緩衝液 (例如透析液和/或置換液) 的施用速率。Regiocit 溶液必須與適當碳酸氫鹽濃度的透析液/置換液搭配使用。

額外進行鈣的輸注是必要的。停止抗凝血治療時，請根據醫師處方調整或停止鈣的輸注。

要根據所欲達到的抗凝血程度設定適當的 Regiocit 溶液劑量，必須監測過濾後血液的游離鈣 (ionized calcium，iCa)、全身性血中 iCa 和血中總鈣濃度以及其他實驗室和臨床參數 (參閱第 4.4 節)。

應定期監測血漿中鈉、鎂、鉀和磷酸鹽的濃度，且應視需要補充。

成人和青少年的 Regiocit 溶液流速：

- 連續性靜脈-靜脈血液過濾
  - 1-2.5 l/h，其中血液流速介於 100 與 200 ml/min 之間。
- 連續性靜脈-靜脈血液透析過濾
  - 1-2 l/h，其中血液流速介於 100 與 200 ml/min 之間。

小兒族群：

新生兒至幼兒 (0 至 23 個月大) 進行連續性靜脈-靜脈血液過濾或血液透析過濾時，Regiocit 溶液應以每公升血流 3 mmol 檸檬酸鹽的劑量為目標。兒童 (2 至 11 歲) 的劑量應根據病人體重與血液流速做調整。

特殊族群：

相較於成人，老年族群的劑量沒有特別變動。

肝功能不全或休克：

在罹患輕度至中度肝功能不全 (例如 Child-Pugh 分數 ≤12) 的病患中，可能需要調降劑量。若患有肝功能不全 (包括例如肝硬化)，應調降檸檬酸鹽起始劑量，因為代謝作用可能不充分 (參閱第 4.4 節)。建議密集監測檸檬酸鹽累積量。由於檸檬酸鹽代謝有限，因此不得對肝功能嚴重下降或肌肉灌流不足引發休克 (例如敗血性休克和乳酸中毒等狀況) 的病患施用 Regiocit 溶液 (參閱第 4.3 節)。

用法

供靜脈使用。Regiocit 溶液需搭配適用於 CRRT 的體外腎臟替代設備使用，限用於預稀釋模式， ，同時應使用專用於檸檬酸鹽抗凝的幫浦，其溶液流速應可根據操作者設定的目標劑量 (mmol 檸檬酸鹽/l 血液)進行自動調整。

唯有能以局部檸檬酸鹽抗凝法進行 CRRT的醫師，或者在其指示下，才可以使用 Regiocit 溶液。

4.3 禁忌症

對活性物質或任何第 6.1 節所列賦形劑過敏。

嚴重肝功能受損。

伴隨有肌肉灌流不足的休克現象。

4.4 使用的特殊警告與預防措施

Regiocit 溶液不適用於直接靜脈輸注。僅限預稀釋、同時搭配適用於CRRT 的體外腎臟替代機器使用。透析機器必須適用於檸檬酸鹽抗凝法。

Regiocit 溶液可加溫至 37°C 以增進病患舒適性。使用前加溫溶液應僅限以乾熱方式進行。溶液不應在水中或微波爐內加熱，因為可能導致患者受傷或不適。只要溶液與容器許可，應於施用前以肉眼查看 Regiocit 溶液是否出現顆粒物質及變色。除非溶液澄清且封條完整，否則請勿施用。

唯有在外包裝和溶液袋未受損時方可使用。使用受到污染的溶液，可能導致敗血病和休克。

考量到 Regiocit 溶液的成分，治療中所使用的其他溶液必須具有適當的碳酸氫鹽濃度。

Regiocit 溶液含有檸檬酸鹽，可影響病患的電解質和酸鹼平衡。治療前與治療期間，應密

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切監控病人的血流動力學狀態、液體平衡、葡萄糖濃度、電解質及酸/鹼平衡。

請密切監測鈉、鎂、鉀、磷酸鹽和鈣。其血中濃度與病人的需要應每日評估數次，包括評估輸注液輸入與所有的輸出。可能需要輸注電解質以彌補任何流失 (請參閱第 4.8 及 4.9 節)。

Regiocit 溶液不含鈣，而且可能因鈣與流出液中的檸檬酸鹽結合而流失，以及/或者發生全身性檸檬酸鹽累積，引起全身性游離性低血鈣症 (systemic ionized hypocalcaemia)。

Regiocit 溶液不含鎂。使用 Regiocit 溶液可能因 CRRT 流出液中的流失而引起低血鎂。由於可能有必要輸注鎂，應對病患進行監測。

Regiocit 溶液不含葡萄糖。施用 Regiocit 溶液可能引起低血糖。應定期監測血糖濃度。

Regiocit 溶液不含鉀。CRRT 之前及過程中務必監測血清鉀濃度。

因代謝不全所導致的檸檬酸鹽累積：

發生肝衰竭 (包括如肝硬化或急性肝衰竭等) 或休克 (請參閱第 4.2 及 4.3 節) 的病人需要格外注意，其檸檬酸鹽代謝可能明顯降低，而使病人處於檸檬酸鹽累積的狀態。如果對這些病人施用檸檬酸鹽來進行血液過濾，建議更頻繁地監控檸檬酸鹽累積情形。如果肝臟和骨骼肌無法代謝掉檸檬酸鹽，則碳酸氫鹽無法產生，而且檸檬酸鹽會累積，隨之產生代謝性酸中毒和低游離性鈣離子血症(ionized hypocalcemia)。監控血液中的游離鈣離子、總鈣及碳酸氫根濃度，可偵測檸檬酸鹽累積的情形。如果發生檸檬酸鹽累積，血液中總鈣與游離鈣離子的比值會上升。如果總鈣/游離鈣離子的比值上升至高於 2.3，檸檬酸鹽緩衝劑應予以減量或停用。如需修正代謝性酸中毒的狀況，則須補充碳酸氫鹽。CRRT 可在沒有抗凝處理的情形下繼續進行，或者必須考慮其他的抗凝方式。

因輸注不當所導致的檸檬酸鹽累積：

不當輸注太大量的檸檬酸鹽 (亦請參閱第 4.9 節)，會造成急性低血鈣症和代謝性鹼中毒，而可能讓病人出現神經與心臟併發症。治療包含檸檬酸鹽輸注中斷和鈣輸注。全身性低血鈣症 (低游離鈣離子) 可能由兩種不同機制所導致：

- *對因檸檬酸鹽引起的經過濾器鈣流失補償不足 (低游離鈣離子和低總鈣)，需調整鈣溶液流速以進行補充；*
- *因肝臟和肌肉中代謝不良所導致的檸檬酸鹽累積 (高總鈣/游離鈣離子比)，需要將 Regiocit 溶液部分或完全改換為不含檸檬酸鹽的置換溶液 (連續性靜脈-靜脈血液過濾)，或者合併降低或停止 Regiocit 溶液的流速同時增加透析液流速，以增加檸檬酸鹽清除效果 (連續性靜脈-靜脈血液透析過濾)。*

全身性高血鈣症

高總鈣合併高游離鈣離子的現象可能因鈣置換溶液過度灌注而發生。如此需降低鈣溶液流速。

高總鈣合併高的總鈣與游離鈣離子比，可能歸因於檸檬酸鹽流速過高或無法代謝足夠的檸檬酸鹽量所導致的檸檬酸鈣累積。如此應該要減少或中斷檸檬酸鹽輸注。

代謝性酸中毒

如果肝臟和骨骼肌無法提供足夠的檸檬酸代謝 (此現象可能發生於肝硬化或急性肝衰竭)，檸檬酸鹽可能會累積。在這些情況中，檸檬酸累積會導致代謝性酸中毒。在這些病人身上，典型陰離子間隙也會隨之提高，反映出檸檬酸離子增加的情形。在多數狀況下，乳酸鹽也會累積。

因無法代謝檸檬酸所導致的代謝性酸中毒，可透過定期代謝監控來及早診斷。

如果在 Regiocit 溶液治療期間發生檸檬酸鹽累積，以及/或者發生代謝性酸中毒或代謝性酸中毒惡化，可能需要調降輸注速率或者停止施用。代謝性鹼中毒

有些病人需要並能耐受高的檸檬酸鹽輸注速率，以將體外循環迴路中的游離鈣離子濃度維持在所需範圍內。Regiocit 溶液含有檸檬酸鹽，有助於整體緩衝負荷。CRRT 溶液或治療過程中施用的其他溶液，其所含的額外碳酸氫鈉 (或緩衝來源) 可能增加代謝性鹼中毒的風險。如果淨檸檬酸鹽施用速率超過維持酸鹼平衡所必需的量，可能發生代謝性鹼中毒 (參閱第 4.2 節)。

此狀況可透過降低血液流速，因而降低進入病人體內的檸檬酸鹽輸注速率來獲得處理。代謝性鹼中毒亦可透過增加透析液流速 (同時維持CRRT 劑量)，以及過濾器後輸注 0.9 % 氯化鈉來獲得處理，或調整 CRRT 溶液的組成。如果病人已經接受大量含有檸檬酸鹽的血液產品，且 CRRT 劑量過低，則亦可能發生伴隨有代謝性鹼中毒與低血鈣症的檸檬酸鹽累積現象。

應對代謝性鹼中毒的病患定期監測血鈣濃度，因為此病症可能使低血鈣加重。

用於肝功能不全的患者

檸檬酸鹽代謝 (轉變成碳酸氫鹽) 在肝功能不全的病患中可能受阻，導致檸檬酸鹽累積。如果對輕度至中度肝功能不全 (例如 Child-Pugh 分數 ≤12) 的病患施用 Regiocit 溶液，務必頻繁監測酸鹼值、電解質、總鈣比游離鈣比值，以及全身性游離鈣，以避免電解質和/或酸鹼不平衡 (參閱第 4.2 節)。Regiocit 溶液不可用於重度肝功能不全患者 (參閱第 4.3 節)。

血液動力學狀態及液體平衡

應於整個程序當中監測病患的血液動力學狀態及液體平衡。

- 若發生高血容量症，可調升針對 CRRT 設備所開立處方的淨超過濾速率，以及/或者可以調降置換液和/或透析液以外溶液的施用速率。
- 若發生低血容量症，可調降針對 CRRT 設備所開立處方的淨超過濾速率，以及/或者可以調升置換液和/或透析液以外溶液的施用速率。

低滲透壓/低張性

Regiocit 溶液相對於標準 CRRT 置換液屬於低滲透壓/低張溶液，因此針對創傷性腦部

傷害、腦水腫或顱內壓上升的病患應謹慎使用。

使用指示必須嚴格遵守。如果輸入連接埠的使用方式不正確，或有其他原因阻礙液體的流動，可能因此造成病人錯誤的體重減輕，且可能引發機器警報。不排除導致發出警報的原因而繼續治療，可能會造成病人受傷或死亡。

僅在溶液澄清且無可見顆粒時使用。

CRRT 導致的鈉清除量與血漿水分鈉含量成正比。整體液體與電解質處理的過程中，為了避免病人的血鈉濃度下降 (低血鈉症)，鈉流失必須獲得平衡 (請參閱第 4.8 節)。施用與 CRRT 相關的透析液及 CRRT 處方以外的溶液時，必須謹慎評估。

4.5 與其他醫藥產品的交互作用以及其他形式的交互作用

在治療期間，可過濾/可透析藥物的血中濃度可能因為被體外過濾器移除而在治療過程中下降。若有必要應執行相應的修正療法，使治療中被移除的藥物達到所需的血液濃度。

Regiocit 溶液的各成分之間預期不會有藥效學藥物交互作用。唯有在溶液的治療使用不當或錯誤時，才可能預期有交互作用 (請參閱第 4.4 及 4.9節)。

然而，含有下列成分的藥品，可預期會有以下交互作用：

- ***維生素 D 及其他維生素 D 類似物，以及含鈣的藥品 (例如用於在接受檸檬酸鹽抗凝血的 CRRT 患者中維持鈣恆定性的氯化鈣或葡萄糖酸鈣) 會增加高血鈣的風險，而且可導致抗凝血作用減弱。***
- ***碳酸氫鈉，可能提高血液中碳酸氫根濃度偏高的風險 (代謝性鹼中毒 – 請參閱第 4.8 節)。***

4.6 生育、懷孕及泌乳

生育：

由於鈉、氯及檸檬酸鹽是屬於人體的正常成分，預期不會影響生育能力。

懷孕及泌乳：

目前沒有在懷孕及泌乳期間使用 Regiocit 溶液的相關臨床資料記錄。Regiocit 溶液只能在有明確需要時施用在懷孕與泌乳女性身上。

4.7 對駕駛與機械使用能力的影響

目前不知道 Regiocit 溶液是否會影響您的駕駛或機械使用能力。

4.8 不良影響

Regiocit 溶液或透析治療有可能帶來不良影響。使用上的特殊預防措施已說明於第 4.4 節中。

在公開文獻中，已有下列不良影響的相關 敘述 (極常見 (1/10)；常見 (1/100 至 <1/10)；不常見 (1/1,000 至 <1/100)；少見 (1/10,000 至 <1/1,000)；極少見 (<1/10,000)；未知 (無法從現有資料中估計)：

代謝與營養失調	
常見	**電解質不平衡，例如低血鎂症 (請參閱第 4.4 節)、低血鈣症 (請參閱第 4.4 及 4.9 節)、高血鈣症 (請參閱第 4.4 節)、低血鈉症 (請參閱第 4.4 節)、低血鉀症 (請參閱第 4.4 節)、低磷酸鹽血症 (請參閱第 4.4 節)**
	酸鹼平衡異常，包括代謝性酸中毒 (請參閱第 4.4 及 4.9 節) 和代謝性鹼中毒 (請參閱第 4.4、4.5 及 4.9 節)
未知	**體液滯留**
	液體失衡，例如脫水 (請參閱第 4.4 節)
血管病變	
未知	**低血壓***
腸胃疾病	
未知	**噁心***
	嘔吐*
肌肉骨骼與結締組織病變	
未知	**肌肉痙攣***

**** 與透析治療相關的不良影響***

4.9 過量

不當施用太高量的置換溶液可能會導致過量，而對病人造成危及生命的情況。如此可能導致肺水腫和鬱血性心臟衰竭 (與體液過多有關)，以及因檸檬酸鹽過多 (與血流有關) 所導致的低血鈣症 (請參閱第 4.4 節) 和代謝性鹼中毒 (請參閱第 4.4 節)。此失調情形需要立即修正，此時應停用置換溶液量，並透過靜脈給予鈣。謹慎補充鈣可逆轉用藥過量的作用。治療過程中密切監測可使此風險降到最低。

檸檬酸鹽代謝受阻 (肝衰竭或休克) 的病人體內，用藥過量可能造成檸檬酸鹽累積、代謝性酸中毒 (參閱第 4.4 節)、全身性總高血鈣 (參閱第 4.4 節) 和游離性低血鈣 (參閱第 4.4 和 4.8 節)，伴隨總鈣/游離鈣比值上升。

因此 Regiocit 溶液應該減量或停用。

如需修正代謝性酸中毒的狀況，則須補充碳酸氫鹽。連續性腎功能替代治療可在沒有抗凝處理的情形下繼續進行，或者必須考慮其他的抗凝方式。

5. 藥理學特性

5.1 藥效學特性

藥物治療組：血液過濾液

ATC 代碼：B05ZB

檸檬酸鹽可用來進行抗凝血，這是因為檸檬酸鹽能夠與離子 鈣 形成複合物，使 其 無法用於凝血系列反應。Regiocit 溶液中，鈉濃度已設定為 140 mmol/l，這是因為重症病人容易出現嚴重低血鈉症。由於溶液不含碳酸氫鹽，氯已設定為平衡陽離子所需的濃度。鈉和氯是屬於人體的正常成分，視為無藥理學活性。檸檬酸鹽是人體的正常代謝物，在克氏循環中 做為 第一中間物質。Regiocit 溶液已除去鉀和葡萄糖。在治療劑量 內不預期會 有因使用 Regiocit 溶液而帶來的毒性作用。

5.2 藥物動力學特性

檸檬酸鹽是人體的正常代謝物，也是克氏循環中的中間物質。只要是低濃度狀態，這個生理途徑就能夠處理掉大量檸檬酸。克氏循環是在粒線體內進行，凡是含有這些細胞胞器的細胞都可以代謝檸檬酸。因此，含豐富粒線體的組織 (如肝臟、

骨骼肌及腎臟) 可以產生並排除大量檸檬酸鹽。

吸收與分布

鈉和氫的吸收與分布，是根據病人的臨床狀況、代謝狀態及殘留腎功能而定。細胞外的檸檬酸鹽可經由一群蛋白質 (即， 血漿 細胞膜檸檬酸轉運蛋白 (PMCTs)) 進行運輸，從血液跨越細胞膜而進入細胞，然後在各種器官與組織中代謝掉。

生物轉化

如上所述，在人體中檸檬酸鹽 是 在稱為克氏循環的中央代謝途徑中 的一個 中間產物。檸檬酸鹽主要在肝臟內快速代謝，但是也可以由其他器官/組織代謝。

排除

任何過量的循環檸檬酸通常經由腎臟排出。

5.3 臨床前安全性資料

除了本藥品說明書於其他章節所提供的資料外，沒有其他認定與臨床安全性有關的臨床前資料。

6. 藥劑特性

6.1 賦形劑清單

注射用水

稀鹽酸 (用於調整 pH 值) E 507

6.2 不相容性

由於欠缺相容性試驗，不得將此醫藥產品與其他醫藥產品混合。

醫師須負責檢查有無可能發生的顏色變化和/或可能發生的沈澱，藉此判斷添加藥物與此藥的相容性。添加藥物之前，請先確認其在此藥中可溶且穩定。

6.3 保存期限

18 個月

6.4 儲存的特殊預防措施

儲存溫度必須低於 30 °C。請勿冷凍。

6.5 容器性質與內容物

容器是一個單一腔室的液袋，由聚烯烴與彈性體的多層薄膜製成。液袋安裝有一個注射連接器 (或插入針連接器) 與一個魯爾接頭 (可供連接合適的血液過濾溶液管路或血液幫浦前管路)。液袋裝有 5000 ml 溶液，而外 層 是由聚合物薄膜製成的透明外包裝加以包覆。每箱裝有兩個液袋和一份包裝說明書。

包裝大小：每箱 2 x 5000 ml

7. 丟棄的特殊預防措施

溶液可經由廢水丟棄，不會危害環境。請遵守以下使用指示：

。處理及施用於病人身上時，應全程使用無菌操作。請於即將使用前才將外包裝自液袋上移除。只有在外包裝未被破壞、所有封條完整且溶液澄清時，才可使用。請用力按壓液袋以測試是否有滲漏；若發現滲漏，因無法確保無菌，請立即棄置該溶液。請於開啟後立即使用溶液，以免受到微生物污染。

I 如果使用魯爾接頭，請以扭轉且外拉的動作來取下帽蓋。利用推入且扭轉的動作，將血液幫浦前管路上的魯爾鎖公接頭，連接到液袋上的魯爾鎖母接頭。請確認連接部分已完全固定且轉緊。此時接頭已開啟。請檢查液體是否自由流動。當血液幫浦前管路與魯爾接頭分離時，接頭將會關閉，且溶液將會停止流動。魯爾接頭是一種無針頭且可擦拭的連接埠。

II 如果使用注射連接器 (或插入針連接器)，請取下可折式帽蓋。將插入針刺入橡膠隔膜。
請檢查液體是否自由流動。添加物質或藥物前，請確保其在 Regiocit 溶液中可溶且穩定，且產品的 pH 範圍適當。不應添加已知或經判定不相容的添加物。務必查閱欲添加之藥物的使用說明及其他相關文獻。添加後，若有任何變色和/或出現沉澱物、無法溶解之複合物或結晶，請勿使用。加入添加物後應徹底混合溶液。務必一律在將溶液袋連接到體外迴路前加入及混合添加物。本溶液僅供單次使用。請棄置所有未使用的部分。

8. 製造廠的名稱與地址

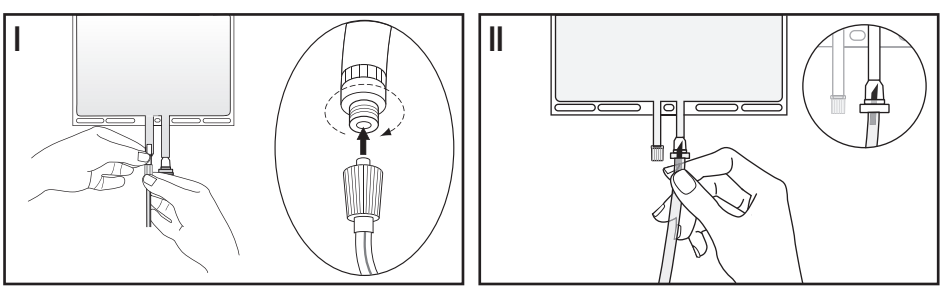
Bieffe Medital S.p.A.
Via Stelvio 94
23035 Sondalo (SO),
Italy

9. 本文修訂日期

2019年10月

藥商名稱: 百特醫療產品股份有限公司

藥商地址: 臺北市大安區敦化南路二段216號15樓



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