

Public Assessment Report

Scientific discussion

**Regiocit, solution for haemofiltration
(sodium chloride and sodium citrate)**

NL/H/2979/001/DC

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This module reflects the scientific discussion for the approval of Regiocit, solution for haemofiltration. The procedure was finalised on 1 October 2014. For information on changes after this date please refer to the module 'Update'.

List of abbreviations

ARF	Acute Renal Failure
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CRRT	continuous renal replacement therapy
CVVH	Continuous Venovenous Haemofiltration
CVVHDF	Continuous Venovenous Haemodiafiltration
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
HITT	Heparin Induced Thrombocytopenia and Thrombosis
ICH	International Conference of Harmonisation
ICU	Intensive Care Unit
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RCA	Regional Anticoagulation
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Regiocit, solution for haemofiltration from Gambro Lundia AB.

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.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a bibliographic application based on the well-established use of this electrolyte-isotonic replacement solution. Numerous haemofiltration solutions exist and are widely used.

Although citrate coagulation is widely used, currently no citrate containing replacement solutions are registered and marketed as a medicinal product (but only as medical device) in the Netherlands or in Europe. Mostly the used citrate solutions are locally manufactured (custom made) and the citrate solutions currently available on the market are concentrated and not indicated for CRRT. The MAH has submitted documentation to support the use of citrate solution not only administered as a separate infusion but also in a premixed solution as in Regiocit.

Scientific Advice was sought in 2007 regarding a question on the applicable legal base. A bibliographical application is appropriate in this case, and the application was submitted accordingly. The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom.

II. QUALITY ASPECTS

II.1 Introduction

Regiocit is a sterile, clear and colourless solution for haemofiltration, free from bacterial endotoxins.

Theoretical osmolarity is 244 mOsm/l and pH ≈ 7.4.

The composition is as follows:

Sodium chloride	5.03 g/l
Sodium citrate	5.29 g/l
Sodium, Na ⁺	140 mmol/l
Chloride, Cl ⁻	86 mmol/l
Citrate, C ₆ H ₅ O ₇ ³⁻	18 mmol/l

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.

The excipients are water for injections and dilute hydrochloric acid (for pH adjustment) E 507.

II.2 Drug Substances

The active substances sodium chloride and sodium citrate are established active substances described in the European Pharmacopoeia (Ph.Eur.). Sodium chloride is a white or almost white crystalline powder or colourless crystals or white to almost white pearls. The substance is freely soluble in water and practically insoluble in anhydrous ethanol. Sodium citrate is a white or almost white crystalline powder or white or almost white, granular crystals, and is slightly deliquescent in moist air. It is freely soluble in water and practically insoluble in ethanol 96%.

The CEP procedure is used for the manufacturers of both active substances. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process

No information was provided on the manufacturing process of sodium chloride as it was assessed by the EDQM when granting the CEP.

The manufacturing process of sodium citrate has been described in sufficient detail. No class 1 solvents or metal catalysts are used. The active substance has been adequately characterised.

Quality control of drug substances

Sodium chloride - The drug substance specification is in line with the Ph.Eur. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two production-scale batches from each supplier.

Sodium citrate - The drug substance specification is in line with the Ph.Eur.. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two production-scale batches.

Stability of drug substances

Sodium chloride - Sodium chloride obtained from one manufacturer is stable for 3 years under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

For the second manufacturer of sodium chloride stability studies were conducted on three full-scale batches stored at 25°C (24 months). Based on the stability data provided the proposed re-test period of 24 months can be granted.

Sodium citrate - Stability data on the active substance sodium citrate have been provided for five production batches stored at 25°C/60% RH (36 or 60 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). Based on the stability data provided the proposed re-test period of 36 months can be granted. No special temperature storage condition is necessary.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients justified and their functions explained. All excipients used are well known. The choices of the packaging and manufacturing process are justified. This product concerns an application submitted under Article 10a (Well-established use) of Directive 2001/83/EC. Therefore bioequivalence studies were not required.

Autoclaving has been chosen as sterilisation method in line with the European guideline "Decision trees for the selection of sterilisation methods". This is appropriate. The product does not contain any added anti-microbiological preservatives. The sterility and bacterial endotoxin tests as per the requirements of European Pharmacopoeia are carried out at release and shelf-life. Overall, the pharmaceutical development has been adequately performed.

Manufacturing process

The drug product is manufactured by preparing water for injections, mixing of the ingredients and filling of the bags. The filled bags are placed on stainless steel trolleys into the autoclave and sterilised. The sterilization process has been adequately validated.

Control of excipients

The excipients comply with their respective Ph.Eur. monographs. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance of solution, identification, pH, aluminium, osmolarity, particulate matter, extractable volume, sterility, bacterial endotoxins and assay. The release and shelf life limits are identical, except for the extractable volume. The drug product specification is acceptable. The analytical methods have been adequately described and validated.

Batch analytical data from the proposed production site have been provided for three pilot-scale batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided five pilot-scale batches stored at 30°C/65% RH (18 months) 40°C/40% RH (6 months) and at 4°C (18 months). The conditions used in the stability studies are not according to the ICH stability guideline, however adequately justified. The batches were stored in Polyolefin 5000 ml bags.

No significant changes were observed. At 40°C and 30°C an increase in permeability is seen. No trends were observed for the other parameters. On the basis of the provided stability data, a shelf life 18 months can be granted. The proposed storage condition of "This medicinal product does not require any special storage conditions. Do not freeze" is justified. Photostability testing will be performed post approval.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Regiocit has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product.

The following post-approval commitments were made:

- The MAH committed to finalise the ongoing stability studies.
- The MAH committed to perform the osmolarity test on each batch of Regiocit until there are sufficient data to justify the performance of the procedure as a skip lot testing.
- The MAH committed to perform photostability testing in compliance with ICH Q1B.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology, Pharmacokinetics, Toxicology

The use of electrolyte-isotonic replacement solutions containing sodium citrate as anticoagulant is well-known. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The non-clinical safety of Regiocit replacement solution was discussed, referring to the available toxicological data on citric acid and experimental studies on citrate and citric acid. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required for this well-established medicinal product.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Electrolytes are unlikely to result in a significant risk to the environment. According to the guideline on the environmental risk assessment of medicinal products for human use, an environmental risk assessment is not needed for this product (EMA/CHMP/SWP/4447/00).

IV. CLINICAL ASPECTS

IV.1 Introduction

Sodium chloride and sodium citrate are well-known active substances with established efficacy and tolerability.

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Clinical efficacy

The use of citrate solution for regional anticoagulation (RCA) administered as an infusion separate from the electrolyte substitution solution before the haemofilter during CRRT-techniques like CVVH, has been in use for more than 30 years and has been proven to be safe and efficacious based on review of documentation in the literature.

Sufficient evidence in the form of (semi)-clinical experience is available to conclude that Regiocit can be used for the claimed use in patients of all ages. It is effective in CVVH for critically ill patients with acute renal failure (ARF) under the auspices of trained personnel if the protocol is ensued.

Continuous haemofiltration techniques sometimes in combination with dialysis (haemodiafiltration) are the preferred treatment for critically-ill patients with acute renal insufficiency in the ICU-department. Veno-venous haemofiltration (CVVH) and veno-venous haemofiltration combined with dialysis (CVVHDF) are often the preferred choice. These techniques are well established since several decades.

From the start these techniques could only be performed using systemic anticoagulation with heparin, with the main purpose to prevent clotting of blood in the extracorporeal circuit.

In case of heparin-induced syndromes like HIT(T) but also in patients with a high bleeding risk the possibility to restrict the anticoagulation to the extracorporeal circuit avoiding systemic anticoagulation with heparin had to be evaluated; the use of citrate solution for this purpose seemed to be most appropriate.

Based on the data from the literature as presented in the clinical overview and regarding more specifically the premixed use of citrate, sufficient support is found to consider the use of citrate solution not only administered as a separate infusion but also in a premixed solution as in Regiocit, efficacious and safe with a positive benefit/risk ratio.

The use of premixed citrate substitution solution may offer some advantages in daily practice although no publications were presented in which the use of premixed citrate solution was compared to the use of a separate citrate solution in a randomized study to support this.

The international KDIGO guideline¹ for CRRT from 2012 supports the use of regional anticoagulation with citrate for acute kidney injury, if no contraindication for citrate exists.

The use of regional anticoagulation with citrate - premixed or separate - is especially indicated when heparins are contra-indicated as in heparin induced thrombocytopenia (and thrombosis) and is to be preferred in case of high bleeding tendency.

IV.3 Clinical safety

Though several metabolic consequences might be induced due to citrate, it is not expected that these will lead to severe negative effects. The procedure with haemofiltration solutions, in combination with citrate, is always performed in hospital settings which indicate that the patient is continuously monitored carefully. Any deviation in the standard values will be noticed timely and derangements can

¹ Kidney disease improving global outcome (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Guideline for Acute Kidney Injury. *Kidney Inter. Suppl.* 2012; 2 : 1-138).

be adequately corrected following the locally available protocols, as clearly stated in the above mentioned adverse effects. The long-term safety is also guaranteed since the haemofiltration solutions equal patient's fluid composition and citrate is metabolized quickly and is subsequently removed from the system.

IV.4 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Regiocit.

- Summary table of safety concerns as approved in RMP

Important identified risks	<ul style="list-style-type: none"> • Citrate intoxication • Metabolic alkalosis • Metabolic acidosis • Hypocalcaemia • Hyponatraemia • Hypomagnesaemia
Important potential risks	<ul style="list-style-type: none"> • Particle embolism
Missing information	<ul style="list-style-type: none"> • None

The member states agree that no risk minimisations measures requiring the use of non-routine pharmacovigilance activities are required.

IV.5 Discussion on the clinical aspects

For this authorisation, reference is made to the well-established use of Regiocit solution for haemofiltration. This has been adequately demonstrated based on literature data. No new clinical studies were conducted. Risk management is adequately addressed. The member states consider the benefit-risk balance of this electrolyte-isotonic replacement solution positive in the proposed indication.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. In the first round 10 participants were included and in the second round 20 participants. Prior to testing an internal test was performed to see if the questions were adequate. Weaknesses of the PL have been identified. Several medical terms were too difficult for the participants of the first round and they were explained or replaced in the second round. Overall, the test results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Regiocit, solution for haemofiltration has a proven chemical-pharmaceutical quality and its use is considered well-established in the approved indication, i.e. 'as replacement fluid for continuous renal replacement therapy (CRRT) using regional citrate anticoagulation'. Adequate non-clinical and clinical overviews have been provided.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that the use of

Regiocit is well-established, and have therefore granted a marketing authorisation. The decentralised recognition procedure was finalised with a positive outcome on 1 October 2014.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached