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Public Assessment Report

Scientific discussion

Sodium Citrate Grifols 136 mmol/L anticoagulant and preservative solution for blood (sodium citrate dihidrate)

ES/H/0972/001/DC

Date: 22/05/2025

This module reflects the scientific discussion for the approval of Sodium Citrate Grifols 136 mmol/L anticoagulant and preservative solution for blood. The procedure was finalised at 19/02/2025.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Sodium Citrate Grifols 136 mmol/L anticoagulant and preservative solution for blood, from Laboratorios Grifols, S.A.

The product is indicated as anticoagulant of whole blood as part of automated donor apheresis and therapeutic apheresis procedures. Therapeutic apheresis includes continuous venovenous haemodialysis (CVVHD), continuous venovenous haemodiafiltration (CVVHDF), sustained low efficiency (daily) dialysis (SLEDD) and therapeutic plasma exchange (TPE) via membrane plasma separation.

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

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

The finished product is a sterile anticoagulant and preservative solution for blood, for extracorporeal use. It contains 136 mmol/l of sodium citrate.

The product is available in polypropylene bags containing 250 mL of the solution and closed by either a twist-off port or with a correct connect port.

II.2 Drug Substance

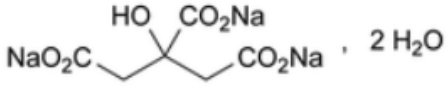
Sodium citrate dihydrate is a known active substance described in the Ph.Eur. The ASMF procedure is used to support the quality of the substance. The assessment of the ASMF is provided in a separate Assessment Report with a confidential annex on the Restricted Part.

General Information

Nomenclature:

Ph.Eur. name:	Sodium citrate dihydrate.
Chemical name:	Trisodium 2-hydroxypropane-1,2,3-tricarboxylate dihydrate
CAS No.:	[6132-04-3]
Molecular formula:	C6H5Na3O7,2H2O

Structure:



General Properties:

White or almost white, crystalline powder or white or almost white, granular crystals, slightly deliquescent in moist air.

Manufacture, process controls and characterisation

Manufacturing process is well described in the ASMF. The specifications of the materials used in the synthesis are sufficient and adequate. The profile of impurities, including residual solvents, of these materials which can influence the quality of the active substance are well defined and controlled. The acceptance criteria for the critical stages and the information on the quality and control of intermediates are adequate.

Specification, analytical procedures, batch analysis

Active substance specifications are considered appropriate and limits justified. Analytical methods are correctly described and validation carried out according to ICH. Batch results support consistent production.

Container closure system

The choice of the container closure system is properly justified. Compliance with the relevant requirements and/or regulations is confirmed.

Stability

Stability studies have been performed in accordance with current guidelines. Protocol, controlled parameters and test methods are considered adequate. The packaging material is similar to that proposed for storage. Proposed re-test period and storage conditions are justified

II.3 Medicinal Product

Description of the product

The finished product is presented as a clear and colourless solution containing 136 mmol/l of sodium citrate as active substance and citric acid monohydrate (for pH adjustment) and water for injection as excipients.

The solution is packaged in polypropylene bags containing 250 mL of the solution and closed by either a twist-off port or with a correct connect port.

Pharmaceutical Development

The development of the product has been described, the choice of excipients is justified and their functions explained.

The physicochemical characteristics of the active substance that may affect the pharmaceutical form are identified and their control strategy is justified.

The proposed method of sterilization has been appropriately justified.

Manufacture of the product

The manufacturing process is fully described and in-process controls are appropriate considering the nature of the product and the manufacturing process. The industrial batch size is well-defined.

Sufficient validation data are provided.

Excipients

Excipients used are well known and of appropriate quality.

None of the excipients is of animal origin.

Product specification, analytical procedures, batch analysis

The finished product specifications are adequate to control the finished product. Provided description and validation data for the analytical methods are adequate. Batch analysis data have been submitted and the results show that the finished product meets the proposed release specification.

Container closure system

The finished product is packaged in in polypropylene bags containing 250 mL of the solution and closed by either a twist-off port or with a correct connect port. The choice of the container closure system is justified considering the nature of the finished product. Compliance with the relevant requirements and/or regulations is confirmed.

Stability

Stability studies have been performed in accordance with current guidelines. The proposed protocol is considered adequate. The packaging material is the same as that intended for marketing. Proposed shelf-life and storage conditions are properly established.

Shelf-life: 2 years.

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

In-use shelf life: Once the container is opened, the solution must be used immediately.

III. NON-CLINICAL ASPECTS

III.1 Critical evaluation of the Non-Clinical Overview

The nonclinical package presented for this procedure relies on scientific literature data. The non-clinical overview based on literature review is considered appropriate.

Pharmacology

Pharmacodynamic properties of sodium citrate are well known. As sodium citrate is widely used and well-known active substance, the non-clinical pharmacology based on literature review is considered appropriate.

Pharmacokinetics

The Applicant has not conducted new non-clinical pharmacokinetics studies with sodium citrate. Information on the absorption of the citrate moiety and on the distribution, metabolism and excretion is documented using references to the scientific literature.

Citrate is a molecule ubiquitously present in the body and serum citrate concentrations are reported to be 70 to 140 µg/mL in rabbits. Whole blood citrate concentrations in dogs are similar to human plasma values, ranging from 9 to 19 µg/mL. Serum citrate is mainly found in the form of trivalent-citrate. It is unbound to plasma proteins because is largely complexed with calcium, magnesium and sodium. For absorption in the small intestine, citrate is thought to use the same transporter as in the proximal tubule of the kidney, a sodium-dependent dicarboxylate transporter (NaDC-1), since it has been found in the intestinal membranes of several animal species.

In another published study which examined the citric acid content of groups of tissues in a single male mouse, it was observed that acid citric was present in bone, whereas soft tissues did not contain significant reserves of citrate.

No metabolism studies were performed for sodium citrate since its metabolism is well established. Citric acid is an intermediate substance in oxidative metabolism involved in the tricarboxylic acid cycle.

Regarding to excretion, animal studies have consistently shown that renal citrate excretion is intricately regulated by systemic and luminal pH, with acidosis promoting reabsorption and reducing excretion, and alkalosis having the opposite effect. it.

No pharmacokinetic interactions with sodium citrate have been reported in animal from scientific literature provided. However, there is sufficient clinical experience in this regard.

Toxicology

As sodium citrate is widely used, and well-known active substance, the Applicant has not provided own studies on the toxicological properties of sodium citrate. Overview based on literature review is considered appropriate.

In repeat-dose toxicity studies in male mice fed with 5% citric acid (approx. 7.5 g/kg/day), decreased growth and lower survival times were observed. Similarly, in rats fed for 2 years with 5% or 3% citric acid, a slight decrease in growth was also observed in the higher dose group, but no tissue abnormalities in major organs. From the lowest dose, a no-observed-adverse-effect level (NOAEL) of citric acid for repeated-dose toxicity was set at 1200 mg/kg/day. Therefore, the overall toxicity results indicate that sodium citrate is well tolerated in different animal species.

No genotoxic potential was evidenced for citrate in three *in vitro* genotoxicity assays (a bacterial reverse mutation (Ames) test, a chromosomal aberrations test in rat bone marrow cells, and a comet assay in mouse fibroblasts). The results of all these literature studies were negative.

In a two-year oral carcinogenicity study performed in rats dosed with 5% citric acid in the diet, no carcinogenic effects (increased incidence of tumours) have been evidenced.

Based on a series of studies in mice, rats, hamsters and rabbits, no effects on reproduction were observed after oral administration of citric acid.

A literature review on local tolerance, including studies in which citric acid was administered in rats and rabbits, concludes that the sensitizing potential of citric acid is low.

III.2 Environmental risk assessment (ERA)

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, sodium citrate is not expected to pose a risk to the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical package presented for this procedure relies on scientific literature data. The clinical overview based on literature review is considered appropriate.

IV.2 Pharmacokinetics

N/A

IV.3 Pharmacodynamics

N/A

IV.4 Clinical efficacy

According to the public literature provided by the Applicant, efficacy of sodium citrate 136 mmol/L as extracorporeal anticoagulant in different automatic apheresis devices to prevent blood coagulation assuring the satisfactory performance of the circuit has been demonstrated. Data from literature cover the two clinical settings where sodium citrate has demonstrated efficacy, such as donation apheresis and therapeutic procedures.

Most of the evidence comes from different modalities of continuous renal replacement therapy (CRRT) and therapeutic plasma exchange (PE). However, with the responses submitted at day 106, the Applicant has provided additional evidence in donation apheresis.

When sodium citrate is infused into the extracorporeal circuit, physiological functions in the donor/patients' blood are modified to maintain the patency of the circuit, preventing clots and complications in donors or patients undergoing automated apheresis procedures. The anticoagulation action provided by sodium citrate is independent whichever apheresis procedures is carried out. However, differences in procedure management will be dependent on different protocols used in the two clinical settings. Differences between both apheresis

procedures have been justified by the Applicant and included in the product information. Information on therapeutic apheresis has been aligned with the recently approved Cifoban (DE/H/6388/001). Specific information on donation apheresis has been included in the product information separately from the therapeutic apheresis. Maximum dose of sodium citrate per donation and dose recommendation in donors at risk of having impaired citrate metabolism to prevent adverse events due to citrate intoxication were requested to the Applicant. With the responses submitted at day 160, the Applicant has recommended in the section 4.2 of the SmPC a maximum infusion rate up to 1.1 mg/kg/min of citrate delivered to the donor lasting up to 90 min. Moreover, considering that donors at risk of having impaired citrate metabolism would not be candidates for donor apheresis, a contraindication in section 4.3 of the SmPC has been included. These adaptations are considered adequate.

IV.5 Clinical safety

Safety profile of sodium citrate when used as anticoagulant into the extracorporeal circuit in automated apheresis procedures is well known. Some amount of sodium citrate can reach donor or patient producing different metabolic consequences (i.e., hypocalcaemia, alkalosis, acidosis and electrolytic disturbances). However, potential unfavourable effects can be closely corrected because these apheresis procedures are automatized, continuously monitored through standardized protocols, and very well controlled by qualified healthcare professionals. Therefore, it is not expected that these issues will lead to severe negative effects as it is supported with the data submitted by the Applicant. Donation apheresis is safer than therapeutic apheresis, therefore, donors are not so closely monitored. However, potential adverse events should be considered. Although paraesthesia is one of the most common adverse events related to sodium citrate administration in automated apheresis procedures, data submitted by the Applicant to establish the frequency of paraesthesia in donation apheresis comes from ACD solutions or sodium citrate solution whose concentration is not reported in the literature. Taking this into consideration, paraesthesia has been classified as unknown frequency.

IV.6 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 Sodium Citrate Grifols 136 mmol/L anticoagulant and preservative solution for blood (sodium citrate dihidrate).

There are neither proposed additional pharmacovigilance activities nor proposed additional risk minimisation measures planned for Sodium Citrate Grifols 136 mmol/L anticoagulant and preservative solution for blood (sodium citrate dihidrate).

IV.7 Discussion on the clinical aspects

Please, see sections IV.4 and IV.5.

V. USER CONSULTATION

The package leaflet 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. The language used for the purpose of user testing the PIL was Spanish.
The 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

Regional citrate anticoagulation (RCA) for extracorporeal circulation has been developed to overcome the problems of using systemic anticoagulation with heparin in a population with a relatively high bleeding risk at baseline or with heparin induced thrombocytopenia and thrombosis syndromes. While there are some options available, such as different medicinal products containing heparin, the use of sodium citrate in different concentrations and formulas (ACD-A, ACD-B) has become widely used for extracorporeal anticoagulation based on its better safety profile, effectivity, shorter half-life (30–60 min) and because its effects (mainly hypocalcaemia) can be reversed more rapidly with calcium.
Sodium citrate infused into the extracorporeal circuit is intended to modify physiological functions in the blood of human beings to maintain the patency of the circuit preventing clots and complications in donors or patients undergoing automated apheresis procedures. The anticoagulation action provided by sodium citrate is independent whichever apheresis procedures were carried out.

Safety profile of sodium citrate when used as anticoagulant into the extracorporeal circuit in automated apheresis procedures is well known and manageable. Donation apheresis is safer than therapeutic apheresis, therefore, donors are not so closely monitored. Therapeutic apheresis procedures are automatized, continuously monitored through standardised protocols and very well controlled by qualified healthcare professionals.

The Applicant has reworded the indication to spell out the two clinical settings where sodium citrate 136 mmol/L has demonstrated efficacy and safety i.e., in automated donation and therapeutic apheresis procedures. The Applicant has provided adequate documentation and information for both clinical settings.

Based on data and the information provided by the Applicant for the proposed indication, the Benefit/Risk ratio is considered positive, therefore, the Application ES/H/0972/001/DC is approvable.