

Public Assessment Report

Scientific discussion

Citrasol HF-CIT-PRE, solution for haemofiltration

**(Sodium chloride, potassium chloride,
magnesium chloride hexahydrate, glucose
monohydrate, sodium-citrate dihydrate)**

NL/H/3018/001/DC

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This module reflects the scientific discussion for the approval of Citrasol HF-CIT-PRE, solution for haemofiltration. The procedure was finalised on 17 February 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
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 Citrasol HF-CIT-PRE, solution for haemofiltration from Dirinco BV.

The product is indicated to be used as electrolyte solution containing tri-sodium-citrate as regional anticoagulant during continuous renal replacement therapy (CRRT).

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

Citrasol HF-CIT-PRE, containing 13,3 mMol/l of tri-sodium-citrate, belongs to the class of hemofiltrates containing electrolytes with a concentration close to the electrolytic composition of plasma. The product is a sterile and pyrogen-free isotonic solution used for reconstituting the extra-cellular liquid during blood purification (haemofiltration) treatments. Citrate is included in the solution to prevent coagulation in the extracorporeal system by chelating ionised calcium and inducing deep hypocalcaemia in the filter. Citrate forms a calciumcitrate complex which partly is lost in the ultrafiltrate. The other part enters the systemic circulation, where it is diluted in the venous blood. The citrate in this solution is metabolised in the body to bicarbonate.

This decentralised procedure concerns a bibliographic application based on the well-established use of this replacement solution for haemofiltration. All of the drug substances have a well established use of more than 10 years in the EEA. Numerous haemofiltration solutions exist and are widely used.

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 Belgium and Luxembourg.

II. QUALITY ASPECTS

II.1 Introduction

Citrasol HF-CIT-PRE is a clear, sterile and pyrogen-free solution containing tri-sodium-citrate as anticoagulant.

The product is packed in 5000 ml PVC bags. All bags are provided with each one Luer-Lock connector and breakable cone and one spike connector for administration of the contents.

Each 1000 ml solution contains sodium chloride, potassium chloride, magnesium chloride, glucose and sodium citrate dehydrate providing the following concentrations expressed in mMol/1000 ml:

Na+	139.9
K+	3.0
Mg++	0.5
Cl -	104.0
Glucose	5.0
Citrate 3-	13.3
Theoretical osmolarity	266 mOsmol/L
pH	4.5 – 6.5.

II.2 Drug Substances

There are no new drug substances in Citrasol HF-CIT-PRE. All the drug substances are described in the European Pharmacopoeia (Ph.Eur.). For glucose monohydrate, sodium chloride, potassium chloride and magnesium chloride hexahydrate valid CEPs have been submitted.

The CEP procedure is used for the active substance. 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

For tri-sodium-citrate sufficient data on the manufacture have been provided. No details on the manufacturing process have been included for the substances for which a CEP is available.

Quality control of drug substance

The drug substance specifications are in line with the Ph. Eur. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data, demonstrating compliance with the Ph.Eur. specifications, have been provided.

Stability of drug substance

The CEPs from magnesium chloride hexahydrate and potassium chloride state a retest period of 36 months. For glucose monohydrate the retest period is 4 years. For tri-sodium-citrate dihydrate stability studies on 3 batches demonstrated that the drug substance is stable, and that a retest period of 48 months is acceptable.

II.3 Medicinal Product

Pharmaceutical development

The formulation is a simple solution of water soluble components. No specific studies are performed in the pharmaceutical development. As the MAH has chosen a non standard sterilization process, a justification for the chosen method in relation to the drug product composition has been provided. The method as such was adequately validated and was already approved for a registered haemofiltration solution. No full validation data with the proposed drug product needs to be provided.

Manufacturing process

A flow chart and a description of the manufacturing process have been provided. The process is straightforward: weighing, bulk preparation, filtration, filling/closures/labelling, overbagging, sterilization, quarantine of sterile product, packaging, quarantine. The manufacturing process in combination with the filling process is validated on a single chamber haemofiltration solution but with a slightly different composition. The manufacturing and filling process were comparable. Given the ease of the process this is accepted.

Control of excipients

Water for injection is used as excipient is manufactured in the plant itself according to methods described in Ph. Eur. monograph water for injection in bulk and is tested regularly according to this monograph. These specifications are acceptable.

Quality control of drug product

The identification reactions for the components in the drug product have been included in the specification. The tests and limits are in line with the Ph.Eur. monograph for solutions for haemofiltration and haemodiafiltration and acceptable.

All the controls on drug product are done according to the official analytical procedure established by the Ph.Eur. Furthermore, all the methods are validated with respect to the presence of tri-sodium-citrate. Batch analysis results for three commercial size batches are included demonstrating compliance with the specification.

Stability of drug product

Three full-scale batches are included in the stability studies. At accelerated 40°C/75% RH (6 months) and 25°C/40% RH long term conditions (24 and 27 months) no trends were observed. Based on the stability data a shelf life of 24 months in 5000 ml PVC bags is acceptable. All bags are provided with one Luer-Lock connector and breakable cone and one spike connector for administration of the contents. The storage conditions are 'Store below 25°C. Do not refrigerate or freeze.'

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 Citrasol HF-CIT-PRE, solution for haemofiltration has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitment was made:

- The MAH committed that the first 3 commercial batches will be followed in stability.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology, pharmacokinetics and Toxicology

Citrasol HF-CIT-PRE replacement solution for hemofiltration contains sodium, potassium, magnesium, chloride, glucose and sodium-citrate. An anti-coagulant does not to have to be infused separately. The use of electrolyte-isotonic replacement solutions containing tri-sodium-citrate as anticoagulant is well-known. A bibliographical application is appropriate. 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 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.

III.2 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 these compounds (EMA/CHMP/SWP/4447/00).

IV. CLINICAL ASPECTS

IV.1 Introduction

All active substances are well-known substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. A detailed, critical analysis of the pharmacology, safety and efficacy has not been included for Citrasol HF-CIT-PRE, and no additional clinical studies have been conducted in this application. General information obtained from published literature, concerning the efficacy of trisodium citrate containing solution has been submitted. However, the efficacy of the electrolyte solution intended for marketing authorization is not discussed. Since these solutions always contain – from a clinical perspective - a comparable amount and composition of electrolytes and are subsequently widespread used for an extensive period of time (since 1961) this did not hinder the assessment.

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

Citrasol HF-CIT-PRE is considered suitable for regional citrate anticoagulation for continuous renal replacement therapy in critically ill adult patients with acute renal failure under the auspices of trained personnel if the local protocol is ensued.

The MAH was requested to justify paediatric use of the proposed HF-CIT-PRE substitution product. Based on a review (Davis 2014¹) in which 11 observational studies have been included, it was shown that circuit clotting was similar for citrate anticoagulation compared to heparin for continuous renal replacement therapy in paediatric patients. With respect to the prevention of circuit clotting, haemofiltration with citrate was more effective than that with heparin in critically ill paediatric patients in a prospective cohort study (Soltysiak 2014²). In this study it was also found that mortality was lower in the citrate-treated patients. Based on this information, paediatric use of the product is considered to be acceptable.

Based on comments made during the assessment procedure, the MAH has added dose recommendations for paediatric patients. The proposed posology recommendations for paediatric and adult patients are based on international treatment guidelines with respect to acute kidney insufficiency. These guidelines recommend a substitution pump flow rate of 25 ml/kg body weight/hour. Hence, based on a patient's weight, the required flow rate (ml/hour) of the HF-CIT-PRE substitution pump can be calculated. Based on this information, the flow rate of the blood and calcium pump are determined. For the determination of the flow rate of the calcium pump, also a patient's ionized calcium plasma level should be taken into account. Calculation of the flow rate of the HF-CIT-PRE substitution pump applied by the MAH is in line with international guidelines and are therefore considered acceptable.

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 hemofiltration 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 metabolic derangements can be adequately corrected following the locally available protocols. The long-term safety is also guaranteed since the hemofiltration 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 Citrasol HF-CIT-PRE.

- Summary table of safety concerns as approved in RMP

Important identified risks	none
Important potential risks	Citrate accumulation due to hepatic failure Citrate accumulation due to inadequate monitoring or bad adherence to the protocol
Missing information	none

The member states agree that there is a need for additional risk minimisation activities for the risk of citrate accumulation. In a separate procedure the educational materials will be assessed by a competent authority in each of the involved member states.

The educational material needs to address the following key elements:

- risk factors for citrate toxicity in patient undergoing Continuous Venovenous Haemofiltration (CVVH) with the use of HF-CIT-PRE
- adequate administration of HF-CIT-PRE
- recommendations and timing for routine metabolic monitoring (e.g. blood investigations)

¹ Davis TK et al, Citrate Anticoagulation During Continuous Renal Replacement Therapy in Pediatric Critical Care. *Pediatr Crit Care Med.* 2014;15(5):471-485

² Soltysiak J et al, Citrate anticoagulation for continuous renal replacement therapy in small children. *Pediatr Nephrol.* 2014 Mar;29(3):469-75.

- the recommended course of actions by the healthcare professionals in case metabolic complications develop, including decreasing or discontinuation of citrate administration and adjustment of replacement fluid, etc., in accordance with the guide for healthcare professionals.

IV.5 Discussion on the clinical aspects

For this authorisation, reference is made to the well-established use of Citrasol HF-CIT-PRE, solution for haemofiltration. This has been adequately demonstrated based on literature data. No new clinical studies were conducted. Systemic anticoagulation with heparin is used to prevent clotting of blood in the extracorporeal circuit. Regional anticoagulation with citrate might be an option for patients in whom heparins are contra-indicated (e.g. in case of heparin induced thrombocytopenia) or in case of a high bleeding tendency. The international guideline of KDIGO (Kidney Disease: Improving Global Outcomes) for CRRT from 2012 supports the use of regional anticoagulation with citrate if no contraindication for citrate exists.

The proposed citrate anticoagulation solution has been introduced on a compassionate use basis in 1997 and is currently being used in over 30 Dutch and Belgian hospitals. This therapy is reported to be well accepted. Paediatric patients have not been included in this program. The MAH has appropriately justified paediatric use of Citrasol HF-CIT-PRE.

The posology recommendations for paediatric and adult patients appear to be based on international treatment guidelines with respect to acute kidney insufficiency, recommending a substitution pump flow rate of 25 ml/kg body weight/hour for continuous renal replacement therapy. Though there is no standard protocol for the determination of these pump flow rates, a local posology protocol might be used as a guide for prescribers. Provided it is made clear that the proposed posology recommendations are based on a local protocol, it is considered acceptable to include these posology recommendations in the SmPC text.

From a clinical point of view, the proposed citrate-based anticoagulation product HF-CIT-PRE is approvable. Risk management is adequately addressed. The member states consider the benefit-risk balance of this 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. Testing was carried out on the English version of the PL. A total of 24 participants were questioned about the leaflet. Prior to the actual user test (main test), a pilot test involving 4 participants was performed. Thereafter the main test was performed with a total of 20 participants (divided in two separate tests with 10 participants). A total of 12 questions were asked which sufficiently addressed the key safety messages. Another four questions have been asked to determine the test person's overall impression of the PL.

After the pilot test some amendments have been made to improve the readability. These have been clearly described in the report. Results of the main testing rounds were good, no additional amendments have been made. More than 90% of the participants were able to find the requested information, and of those, more than 90% were able to understand the information that was found and would act appropriately. Based on the test results the member states agree to the conclusions of the readability report. The package leaflet is acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Citrasol HF-CIT-PRE, solution for haemofiltration has a proven chemical-pharmaceutical quality and its use is considered well-established in the approved indication, as electrolyte solution containing tri-sodium-citrate as regional anticoagulant during continuous renal replacement therapy (CRRT).

Adequate non-clinical and clinical overviews have been provided.

In the meeting of the Medicines Evaluation Board of the RMS on 13 November 2013, the application was discussed. Based on the clinical overview initially submitted the Board required further justification for use in paediatric patients. The MAH provided adequate additional literature data to address the concerns, and also added dose recommendations for use in children.

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 Citrasol HF-CIT-PRE is well-established, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 February 2015.

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