COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

T2

Public Assessment Report

Scientific discussion

Citrasol HF-CIT-POST, solution for haemofiltration

(sodium chloride, calcium chloride dihydrate, potassium chloride, magnesium chloride hexahydrate, glucose monohydrate)

NL/H/4122/001/DC

Date: 15 August 2019

This module reflects the scientific discussion for the approval of Citrasol HF-CIT-POST, solution for haemofiltration. The procedure was finalised at 12 July 2018. 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
CVVH	Continuous Venovenous Haemofiltration
EDMF	European Drug Master File
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
RCA	Regional Anticoagulation
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
UF	Ultra filtrate

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-POST, solution for haemofiltration from Dirinco BV.

The product is indicated for continuous renal replacement therapy (CRRT) in combination with regional citrate anticoagulation of the extracorporeal circuit.

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

Citrasol HF-CIT-POST, solution for haemofiltration is a sterile pyrogen-free electrolyte replacement solution, industrially manufactured for continuous haemofiltration techniques more particularly continuous veno-venous haemofiltration (CVVH) in patients with acute renal insufficiency. It is used in combination with tri-sodium citrate as anticoagulant, with the purpose to perform regional anticoagulation (of the extracorporeal circuit) avoiding systemic anticoagulation.

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-POST is a clear, sterile and pyrogen-free solution for haemofiltration with pH 4.5 - 6.5.

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

The excipients are sodium lactate 50% and water for injections.

Each 1000 ml solution contains sodium chloride, potassium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate and glucose monohydrate providing the following concentrations expressed in mmol/1000 ml:

Na^+	109.4
K^+	2.1
Ca^{2+}	1.8
Mg^{2+}	0.5
Cl^-	113.2
$Lactate^-$	3.0
Glucose	5.80

II.2 Drug Substances

Citrasol HF-CIT-POST contains sodium chloride, calcium chloride dihydrate, potassium chloride, magnesium chloride hexahydrate, glucose monohydrate, sodium lactate 50% and water for injections. All active substances are described in the European Pharmacopoeia (Ph.Eur.).

The CEP procedure is used for the 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 Ph.Eur.

Sodium chloride
Sodium chloride is a white or almost white crystalline powder or colourless crystals or white to almost white pearls. It is freely soluble in water, practically insoluble in anhydrous ethanol.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for three years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Calcium chloride dihydrate
Calcium chloride dehydrate is a white to almost white, crystalline powder. It is freely soluble in water, and soluble in 96% ethanol.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 48 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Glucose monohydrate
Glucose monohydrate is a white or almost white crystalline powder. It is freely soluble in water, and sparingly soluble in ethanol 96%.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 48 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Potassium chloride
Potassium chloride is a white or almost white crystalline powder or colourless crystals. It is freely soluble in water, and practically insoluble in anhydrous ethanol.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance
The active substance is stable for 36 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Magnesium chloride hexahydrate
Magnesium chloride hexahydrate is a colourless hygroscopic crystal. It is very soluble in water, freely soluble in ethanol 96%.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 36 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. Citrasol HF-CIT-POST is an infusion solution for haemofiltration filled in a 5000 ml PVC bag. For the composition of the drug product reference is made to the literature. The proposed composition differs slightly from the composition described in literature, with slight different amounts for certain components (e.g. Na^+ 109.4 vs 109.5 mmol/l, K^+ 2.1 vs 2.0 mmol/l, Cl^- 113.2 vs 116.2 mmol/l). These slight changes are however within the allowed variation in the drug product (i.e. the drug product release specifications). The formulation is a simple solution of water soluble components. Pharmaceutical development has been adequately performed.

Manufacturing process
A flow chart and a description of the manufacturing process are provided. 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. This is accepted.

Control of excipients
All excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for solutions for haemofiltration and haemodiafiltration. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Three full scaled batches are used for the stability studies. At accelerated (40°C/75% RH for 6 months) and long term conditions (25°C/40% RH for 27 months) no trends were observed. On the basis of the data submitted a shelf life was granted of 24 months with the storage conditions “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-POST has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology, pharmacokinetics and toxicology

Citrasol HF-CIT-POST replacement solution for haemofiltration contains sodium, potassium, magnesium, chloride, glucose and sodium. An anti-coagulant does not to have to be infused separately.
The use of the electrolyte-isotonic replacement solution 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)

A formal Environmental Risk Assessment has not been carried out. 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 (EMEA/CHMP/SWP/4447/00).

IV. CLINICAL ASPECTS

IV.1 Introduction

The active substances are well-known 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 Pharmacokinetics

Since the composition resembles that of human plasma, a pharmacokinetic reaction is not to be expected. The haemofiltration fluid replaces an equal amount of electrolytes and water as being removed. It is possible that certain desired corrections are made by means of variation in the concentration of certain electrolytes and/or osmotic substances. Citrate is a buffer and is converted in the human body in the Krebs cycle.

Citra-HF-POST, and Citra-HF-pre
No negative pharmacokinetic reactions are to be expected for the Citra-HF products since they resemble the various blood electrolytes in a (near) physiological concentration. It is nearly isotonic compared to blood, about 300 mOsm/l. The composition ensures that the loss of volume is compensated by an equally solution and as well has no consequences on the patients' metabolic status. The pharmacokinetic reactions to be expected are, as desired, the same as in a healthy individual.

Tri-sodium-citrate 13%
Most of the citrate is lost in the ultra filtrate (UF) as a calcium-citrate complex. The other part enters the systemic circulation, where it is diluted in the venous blood. Citrate ions are mainly metabolized in skeletal muscle and liver tissue in the Krebs cycle. Systemic citrate acts as a buffer by conversion to citric acid yielding sodium-bicarbonate.

Na_3citrate + $3H_2CO_3$ <--> Citric acid + $3NaHCO_3$

The metabolism of each citrate molecule generates two to three molecules of bicarbonate. Citrate ions bind to positively charged metal ions like calcium, magnesium, iron, zinc, copper, and manganese. A shortage of these ions can subsequently be expected. Citric acid has a plasma half life of five minutes and is readily metabolized to CO_2 and H_2O in the citric acid (Krebs) cycle in liver, kidney and muscle cells, or is metabolized to glucose (gluconeogenesis). In the systemic circulation, ionized calcium rises again due to the dilution of the extracorporeal blood, the replacement of calcium and the liberation of calcium from the calcium-citrate complex when citrate is metabolized. The amount of citrate entering the systemic circulation depends on the amount of citrate infused and its loss in UF. Clearance of citrate by ultrafiltration is equal to clearance of urea. In a recent publication, skeptical researchers enunciate that citrate metabolism has never been evaluated systematically in hemodialysis patients, and that it remains to be shown that citrate is cleared adequately in the presence of renal dysfunction. Their study compares the pharmacokinetics of citrate in long-term hemodialysis patients with minimal residual function with that in patients with normal renal function by using a standardized citrate infusion protocol. They conclude that basal and peak citrate concentrations were similar in both groups as accounts for citrate clearance, which was similar in patients with renal failure and controls. Effects on pH were minimal and did not differ between groups. None of the patients developed complications from citrate infusion. They conclude that compared with controls, citrate clearance and metabolism in long-term hemodialysis patients is not impaired, and no significant acid-base disorder occurred during citrate anticoagulation.

Interactions with haemofiltration solutions are virtually non-existent as the solutions resemble the human plasma. However, the haemofiltration process itself implies significant loses of plasma volume due to convective transport. This loss of plasma volume might interfere with other drug treatments, as it might significantly lower the plasma levels of drugs, especially those which are predominantly non-protein-bound.

IV.3 Pharmacodynamics

General pharmacodynamics

Taken the composition of substitution fluids into account, a pharmacodynamic reaction is not to be expected. Substitution fluids for haemofiltration are sterile, pyrogen-free solutions composed of electrolytes solved in water, made for injection. The composition can be adjusted to the desired value of hypertonicity by addition of salts or glucose. Citrate chelates calcium and subsequently forms citrate-calcium-complexes. In the human body this might cause a hypocalcaemia. Citrate also chelates magnesium which consequently might result in a hypomagnesia.

Citra-HF-Post is an infusion solution for haemofiltration containing the various blood electrolytes in a (near) physiological concentration. It is nearly isotonic compared to blood, about 300 mOsm/l. The composition ensures that the loss of volume is compensated by an equally solution and as well has no consequences on the patients' metabolic status. On the contrary, haemofiltration solutions ensure that the metabolic status of the patient is continuously equal. Both haemofiltration solutions are supplemented with chloride ions to

achieve a neutral electrochemical balance. The substitution solution also utilizes lactate as a (blood) buffer. This can occasionally be problematic in patients with severe lactic acidosis. This can be circumvented by the use of bicarbonate as an alternative buffer.

Calcium is added to the solution Citra- HF-Post in a concentration of 1.8 mmol/l. The additional calcium compensates the loss of (systemic) calcium in the ultra filter, bound to citrate, during the haemofiltration procedure. This prevents a negative pharmacodynamic reaction since the systemic calcium concentration will be maintained.

Tri-sodium-citrate has mild calcium-chelating properties. The infused citrate binds the free calcium ions in the extracorporeal circulation and forms calcium-citrate complexes, thus inducing a deep hypocalcaemia before the filter. Subsequently, the absence of calcium ensures a decrease in fibrinogen levels and platelet counts which results in anticoagulation of the extracorporeal filters and circuit. The complex is partly lost in the UF. The other part enters the systemic circulation, where it is diluted in the venous blood and subsequently does not induce any reaction anymore. Though anticoagulation with citrate has no systemic consequences on anticoagulation, it has metabolic consequences. During citrate CVVH, the citrate infusion rate and the loss of citrate by filtration and metabolism of citric acid influence acid-base balance. As a result, during citrate haemofiltration the composition of the substitution fluid has to be adjusted, metabolic monitoring is necessary and, since systematic anticoagulation does not occur, the patient should receive normal thrombosis prophylaxis unless contraindicated.

IV.4 Clinical efficacy

Scientific background that support the investigation of this pharmaceutical for the stated indications as well as a description of the development program, is not available since no new drug substances are involved in Citra-HF-Post and no additional, non-clinical, clinical, pharmacological or toxicological studies have been conducted in animals or humans for these products manufactured by the MAH. The use of electrolyte-isotonic replacement solution like Citra-HF-Post, and citrate for blood anticoagulation of the haemofiltration circuit, is extensively documented in literature and proven effective and safe for clinical use.
The efficacy of the electrolyte solution will not be discussed since these solutions always contain a comparable amount and composition of electrolytes and are subsequently widespread used for an extensive period of time.

Since Citra-HF-Post (in combination with Citra-13%) is only used in hospital settings, there is little comparative literature or explicit clinical studies reported. The literature available though, is quite persistent. The patients described in literature for this kind of pharmaceutical are exclusively critical ill patients in ICU, generally with acute renal failure and are suspected to have an increased risk of internal bleedings. There is a highly heterogenic patient population. This is consistent with the population of interest for the use of this pharmaceutical.

Inhibition of calcium can be achieved by the pre-filter infusion of citrate. Citrate prevents clotting by chelating ionized calcium and inducing deep hypocalcemia in the filter. Citrate binds to the free calcium ions, creating calcium-citrate complexes. For optimal anticoagulation, citrate dose is adjusted to blood flow. A target concentration of citrate of 3-5 mmol/l should be attained before the filter to reach an ionCa concentration of less than 0.35 mmol/l, necessary to inhibit coagulation. Several formulations of citrate are reported with varying tri-sodium citrate solutions. A lower concentration of citrate demands a higher volume to be infused and thus to be stored. Since the citrate solution prescribed, 13%, is relatively high, less citrate-solution needs to be infused and thus stored, which makes it easier to handle. Besides, this system does not require a high infusion rate of substitution fluid in order to administer sufficient citrate for efficient anticoagulation and there is no demand for a high rate of ultrafiltration for maintenance of fluid balance. Altogether this accounts for a non-invasive haemofiltration therapy.

A range of literature and studies, from the eighties till nowadays, describe the efficiency of citrate as an anticoagulant in CVVH. Moreover, in 1961 citrate is already described as an effective anticoagulant during hemodialysis. Most citrate based-CRRT literature states effective use in especially critically ill ICU patients (elderly and children) with an increased risk of internal bleeding. Several of these however, also advise that citrate should also be used in non-critical patients. Citrate is well tolerated and proved superior in preventing bleeding events and clotting problems. Alternatives, like citrate, to the “golden-standard” heparin anticoagulation should be made available for (high) risk patients requiring acute extracorporeal therapy.

Although literature concerning the efficacy and safety of citrate/ heparin/ or other anticoagulantia-based CVVH is extensive, detailed studies are lacking. Various publications and studies compare systemic heparin anticoagulation with local citrate anticoagulation, but extensive clinical studies are scarce. Most of the literature describes observational or descriptive studies or research is limited to theoretical or database information. Most studies describe the feasibility of their method, some compare circuit life and bleeding with historical or contemporary nonrandomized controls. Besides, the quality of the studies in general is low in terms of size, comparability of groups, follow-up, etc. A review from 2006 by Oudemans-van Straaten, visualizes this aspect. They carried out a systematic review of the literature published before June 2005 concerning CRRT in terms of implementation, efficacy and safety. They identified only two small randomized studies comparing unfractionated heparin to citrate. They state that future trials should be randomized and should have sufficient power and well-defined endpoints to compensate for the complexity of critical illness-related pro- and anti coagulant forces. Still, they conclude that regional coagulation (RCA) with citrate is useful and is worthwhile by means of reducing bleeding risk in critically ill patients. Despite the lack of extensive quality research, the quantity of observational, descriptive, (small) clinical, etc. studies is large. The conclusions of these studies are generally in line and, as far we know, none describes extremely negative (side)-effects of the use of citrate. Citrate anticoagulation is a safe and particularly effective anticoagulant in CVVH in (critically ill) patients if performed by educated health professionals guided by a strict protocol. In, among others, a pilot study combined with a retrospective

analysis, it is additionally concluded that regional citrate anticoagulation in CVVH is not only safe and effective, but also relatively simple to perform. The literature search found enough evidence in the form of (semi)-clinical experience to conclude that Citra-HF-Post (with or without separately infused Citra-13%) can be safely used for the claimed intended use. It is effective in CVVH for critically ill patients with acute renal failure under the auspices of trained personnel if the protocol is ensued. Undesired effects and hazards (see safety aspects) of this technique can subsequently be avoided or easily corrected by adjustment of the blood flow, UF flow, citrate flow, calcium flow and substitution fluid flow.

IV.5 Clinical safety

General CCVH

Side effects of haemofiltration solutions are not relevant as all ingredients are of a physiological nature. The safety of this type of product is completely subordinate to the safety of the technical procedures involved. The procedure of haemofiltration in general can lead to technical complications (occlusion of catheter or haemofilter). In a review from 2000 however, it is stated that CRRT is easy to conduct, safe and flexible once the appropriate training of nursing and medical staff has been achieved.

General serious adverse effects of citrate used in CVVH

Part of the citrate released in the extracorporeal system is lost in the UF and the other part enters the systemic circulation. Citrate acts as a buffer by conversion to citric acid, thereby generating sodium bicarbonate. Therefore, citrate has no effect on systemic coagulation.

Hazards associated with citrate are depending on metabolism and infusion rate. Hazards include the following metabolic complications for as well tri-sodium-citrate infused separately (pre-filter) from the infusion of the electrolyte solution (post-filter) as in Citra-HF-Post:

- Accumulation of citrate

Citrate ions are mainly metabolized in skeletal muscle and liver tissue. In cases of severe hepatic failure combined with severe shock, or in certain (rare) metabolic diseases, the metabolism of citrate may run short leading to high citrate concentrations in the systemic blood circulation, which on its turn may endanger the patient. Accumulation can occur as free citrate or as calcium-citrate complexes. The main dangers are those of hypocalcemia (see below). When free citrate accumulates, there is a rise in anion gap. Accumulation of calcium-citrate complexes will increase the total-to-ionised calcium ratio. A ratio of more than 2.5 is indicative for citrate accumulation. Inadequate metabolism of citrate may also lead to metabolic acidosis. In case of accumulation, the haemofiltration solution needs to be converted to bicarbonate-buffered CVVH with an alternative form of anticoagulation.

Objective features of citrate toxicity include myocardial depression, arrhythmias and systemic alkalosis which may or may not include an anion gap. Proper surveillance of the rate of citrate administration (parallel to UF flow), monitoring and correction of systemic

ionized calcium may obviate these effects. Accordingly, special attention needs to be given for patients with hepatic and/or skeletal muscle failures and caution must be exercised in treating these patients. Specialists have to check the patient's status thoroughly, in order to avoid an accidental citrate overdose. Since CVVH is only performed in critically ill patients in ICU by classified personnel, patients are diagnosed carefully and it is not to be expected that a hepatic failure will be overseen. In case of accumulation, reduction or caesurae of citrate infusion or additional supply of calcium is required.

- Metabolic Acidosis

If citrate accumulates, since acid accumulates or if the liver fails to metabolize citrate, metabolic acidosis develops. Another possible cause is that the buffer replacement is not well compensating for buffer loss by filtration or metabolic acid production. In the first scenario, citrate infusion needs to be stopped; the second cause can be treated by replacement of more (bicarbonate-) buffered solution.

- Metabolic alkalosis

Metabolic alkalosis occurs due to the metabolisation of citrate by the liver and muscle cells. Metabolisation of each citrate molecule generates two to three molecules of bicarbonate. With regional citrate anticoagulation some studies report up to 38% of metabolic alkalosis requiring treatment.

Excessive citrate administration (by declining UF flow and/or increasing citrate flow), can cause metabolic alkalosis due to citrate accumulation and its subsequent metabolism to bicarbonate, and symptoms due to depressed systemic ionized calcium levels. These side effects can be avoided by judicious administration of systemic calcium, monitoring of the ionized calcium levels and the acid-base parameters of the patient. These values are regularly obtained in all critically ill patients in intensive care units. If metabolic alkalosis does not decline rapidly, the filter needs to be changed (to increase UF flow), more buffer-free solution needs to be added, or citrate treatment must be stopped.

There are few reports in the literature of severe metabolic alkalosis induced by regional citrate anticoagulation. This is a complication which will mainly occur when a separate tri-sodium citrate pump is used without coupling to ultrafiltration. Metabolic alkalosis in citrate buffered replacement solution is a rare complication. One single prospective study observed alkalosis in more than 50% of the patients though. The reason of these extremely high and exceptional findings is probably due to administration problems. A trend towards metabolic alkalosis is often seen in the first hours of CRRT, but in almost all cases, alkalosis could simply be reversed by increasing the dialysate flow rate.

- Hypocalcaemia

Because citrate ions bind to positively charged metal ions like calcium, magnesium, iron, zinc, copper, and manganese, these ions are also partly removed in the extracorporeal filter, leading to a net removal of calcium ions and other metal ions from the patient's blood. Calcium bound to citrate is lost by filtration. As a result, hypocalcemia (and/or hypomagnesemia) and/or shortages of other metal ions may be induced in the patient as

soon as there is an increased loss of calcium. Hypocalcaemia may induce life-threatening complications in the patient. As soon as hypocalcemia is diagnosed, citrate infusion needs to be stopped or the supply of calcium needs to be increased. Since most critically ill patients have some degree of hypocalcaemia, target ion Ca should be subnormal, around 1 mmol/l.

- Hypernatremia

Hypernatremia can occur due to a relative high citrate to UF flow; or a declining UF flow while citrate flow is constant; or citrate flow is high in relation to blood flow. This results in an increase of citrate in the patient. Since tri-sodium-citrate contains numerous sodium ions, it flows over into the systemic circulation of the patient significantly increasing the blood sodium concentration. As a result, hypernatremia may occur. There is consequently metabolic alkalosis as well. This can be corrected by ensuring a constant blood, UF and citrate flow or by switching to a buffer-free solution. In general, if the UF flow is less than 1500-2000 ml (depending on blood and citrate flow), the filter needs to be replaced. Probably the filter is clogged which results in a decline of the UF flow.

- Hyponatremia

Hyponatremia is caused due to the opposite possibilities mentioned in the previous described condition of hypernatremia. Since this solution contains no buffer, metabolic acidosis is probably present as well. The treatment consists of the substitution of sodium or a bicarbonate-buffered solution.

- Hypomagnesia

Because citrate ions bind to positively charged metal ions like calcium, magnesium, iron, zinc, copper, and manganese, these ions are also partly removed in the filter, leading to a net removal of magnesium ions and other metal ions from the patient's blood. As a result, hypomagnesemia (and/or hypocalcaemia) and/or shortages of other metal ions may be induced in the patient. Hypomagnesemia may induce life-threatening complications in the patient. The treatment consists of supply of magnesium together with calcium. Hypomagnesia is generally not seen, probably since plasma magnesium is corrected by a shift from the intracellular compartment. In addition, Citra-HF-Post replacement fluid contains magnesium. 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 immediately and can be easily corrected, 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.

<u>Paediatrics</u>

RCA with citrate has been shown to be a safe and effective modality for CRRT in critically ill children as well. There are no prospective interventional or randomized studies comparing regional versus systemic anticoagulation in the paediatric population. However, eleven retrospective and prospective observational cohort studies on citrate anticoagulation have

appeared (see separate list as addendum). These studies have recently been summarized by Davies et al. This review shows that in the paediatric population regional citrate anticoagulation is effective, provides equivalent circuit survival and decreases bleeding compared with heparin anticoagulation. After this review, one more clinical study has appeared including paediatric patients with liver failure. Finally, the sodium citrate 13% prefilter in combination with the Citrasol HF-CIT-POST substitution fluid post-filter is presently used in the paediatric population in the Netherlands.

The age of the included children varied between new-born and 17 years. Blood flow was 3-6 ml/kg/h and dialysis dose about 2000 ml/1.72 m^2 per kg per hour. Similar to the adult population, citrate dose was adjusted to blood flow (2.5 - 3 mmol/l) and subsequently titrated on measured post-filter ionized calcium (0.2 - 0.5 mmol/l, with the higher targets in patients with liver failure). Several kinds of substitution fluids were administered pre- or post-filter. This strategy has appeared to be safe, even in paediatric patients with liver failure. In this population, citrate accumulation, as defined by a ratio of total to ionized calcium >2.5 for >48 hours, was common, occurring in 35/51 patients (93/1000 CRRT days), but was not associated with an increase of adverse events. Interventions included decreasing the dose of citrate, increasing diffusive clearance, adjusting ultrafiltration rate and transiently stopping citrate. Treatment was interrupted in only two patients, for less than six hours each. Although the risk of citrate accumulation is higher in the patients with liver failure, citrate anticoagulation is still needed because of the high bleeding risk in the liver failure population. The Sodium Citrate 13% fluid is presently used in the Netherlands in a dose of 2 - 4 mmol/l blood flow, adjusted to post-filter ionized calcium concentrations. Thus, regional citrate anticoagulation is commonly employed in the paediatric critical care population requiring CRRT.

<u>Posology paediatrics</u>
Based on the above provided information for paediatrics, an example of a local protocol could look like:

Patient weight	Blood pump ml/min. (3 – 6 ml/kg)	Citrasol HF-CIT-POST ml/hr (25 ml/kg)	Sodium citrate 13% ml/hr
10 kg	30	250	10
20 kg	60	500	20
30 kg	90	750	30
40 kg	120	1.000	40

The citrate dose can be adjusted based on the post-filter ionized calcium concentration. Accumulation of citrate has to be guarded by the total to ionized calcium ratio. This value should not exceed 2.5 for more than 48 hours. If the ratio remains higher, citrate dose should be reduced or discontinued.

In conclusion, as in the adult population, citrate anticoagulation is an interesting option in critically ill children, especially in those with an increased risk of bleeding, e.g. after recent

surgery or with coagulopathy. Complications of citrate anticoagulation can be avoided when using a strict protocol and by creating understanding by the health care professionals.

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 Citrasol-HF-CIT-POST.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• Citrate overdosage due to inadequate monitoring or bad adherence to the protocol • Citrate accumulation due to hepatic failure
Important potential risks	--
Missing information	--

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 will address the following key elements:

- risk factors for citrate toxicity in patient undergoing citrate-based CVVH with the use of Citrasol HF-CIT-POST
- adequate administration of Citrasol HF-CIT-POST
- recommendations and timing for routine metabolic monitoring (e.g. blood investigations)
- the recommended course of actions by the health care providers in case metabolic complications develop including decreasing or discontinuation of citrate administration and adjustment of replacement fluid, etc.) in the health care providers guide

IV.7 Discussion on the clinical aspects

The general physiological principles of the common infusion solution have been described. An overview of literature for the use of citrate based anticoagulation in CVVH has been provided. This overview has already been used for the registration of Citra-HF-Pre (NL/H/3018/001/DC), which has been approved based on these data. Several additional references, most notably a reference including 200 patients treated with post-dilution CVVH randomised to citrate or nandroparin (Oudemans-van Straten et al., 2009) have been provided. Literature of experience with this method is already available from 1987 onward and has been reviewed by some authors. Review articles recommend to specifically use this method for patients with increased risk for bleeding, and consider it a treatment option when heparin cannot be used (e.g. when HIT (heparin induced thrombocytopenia) occurs)

which could be considered reasonable based on the pharmacological properties. Some guidelines even recommend this therapy for wider use, e.g. the KDIGO guideline on AKI 2012 Section 5 also recommends this method in patients without increased bleeding risk or impaired coagulation. This recommendation is based on studies comparing this method of regional citrate anticoagulation to unfractioned heparin anticoagulation only including patients without bleeding risk, although the studies are generally hampered by study size and study methodology (except for a more recent study of 200 patients as mentioned). These studies concluded that the use of citrate is associated with a lower risk of bleeding and longer filter survival. Provided the method is performed by educated health professionals guided by strict protocols. Although, unfractioned heparin remains currently the most widely used anticoagulant during CRRT.

The current Citra-HF-Post uses a method in which a separate containing citrate solution is added to the extracorporeal circulation pre-filter and a calcium containing substitution solution is added extracorporeal post-filter. This is different from the registered Citra-HF-Pre, where the citrate is part of the substitution solution and is added to the extracorporeal circulation pre-filter, where calcium has to be added i.v.. Both methods are used in clinical practice, and any differences from an efficacy point of view between both methods only relate to different aspects of simplicity of use. Any data on comparison of both methods appear to be lacking. From literature, current method using calcium containing solutions have been explicitly described in some studies (Evenepoel 2002; Gupta 2004).

For the Citra-HF-Pre product, a paediatric posology (and thus indication) has been approved, after further clarification in second and third round during the registration procedure. Also for Regiocit a paediatric posology has been included. For the Citra-HF-POST product, a paediatric posology has been proposed justified by some literature data.

The general safety aspects related to CVVH therapy have been discussed. The substitution solution is an isotonic solution with human plasma with no particular safety issues. For citrate, several safety issues could occur including metabolic acidosis, metabolic alkalosis, hypocalcaemia, hypernatremia, hyponatremia, or hypomagnesia. These are predominantly associated with imbalances in flow-rates, inappropriate monitoring and/or specific patient conditions not accounted for. The product is to be used in a hospital in specific ICU setting. Under these circumstances, safety aspects will be minimised if strict procedures/protocols are followed and are performed by well educated professionals, also because of the complexity of the procedure. If imbalances occur these can be observed timely and generally be corrected adequately.

A specific risk for the use of citrate is in patients with severely impaired liver function or shock with muscle hypoperfusion, both in which citrate may accumulate in the body. Warning statements have been included in the SmPC for these circumstances.

Overall, a similar safety discussion as for the registered Citra-HF-Pre has been presented for the Citra-HF-Post. The safety discussion was considered appropriate for the Citra-HF-Pre and

can therefore be considered appropriate for the Citra-HF-Post as safety aspects can be considered generally similar between these products.

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. The test consisted of: a pilot test with four participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Citrasol HF-CIT-POST, solution for haemofiltration has a proven chemical-pharmaceutical quality. Citrasol HF-CIT-POST, solution for haemofiltration is an effective drug and its use is considered well-established in the approved indication. The benefit/risk balance is considered positive.

Adequate non-clinical and clinical overviews have been provided.

The Board followed the advice of the assessors.

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 essential similarity has been demonstrated for Citrasol HF-CIT-POST with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 July 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/4122 /IB/001/G	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product	--	2-6-2019	Approval	--