VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Acute renal failure (ARF) is a sudden decrease in kidney function. It is a life-threatening condition and often occurs as a complication to critical illness, including trauma or sepsis. The patients often have various underlying conditions, including liver disease / decreased liver function, multiple organ failure, bleeding tendencies and heart conditions, etc. More than 50% of ARF patients die, mostly due to their underlying condition.

In Europe it is estimated that between 1 to 6 persons out of 10.000 may experience ARF requiring treatment with dialysis.

VI.2.2 Summary of treatment benefits

No specific drugs are available for treating ARF. The main treatment option is to support the kidney function as much as possible, which is done in dialysis (“Renal replacement therapy” (RRT)). In dialysis, the patient is connected via blood tubes to a dialysis machine equipped with a filter, which functions as an “external kidney”. During dialysis excess fluid and soluble substances are removed. Some of the fluid removed is replaced by dialysis fluids (so-called replacement solutions).

Various methods of dialysis are available, and one of them is continuous dialysis (Continuous Renal Replacement Therapy (CRRT)), where the patient is placed on continuous dialysis for an undefined period of time.

One of the main challenges in continuous dialysis is to prevent the blood from clotting in the circuit, i.e. in the tubing that connects the patient to the machine, or in the filter on the machine. If the blood clots, the circuit is blocked and the treatment needs to be discontinued and a new circuit set up before the treatment can be continued. During this interruption, the patient is not receiving any treatment.

To prevent the blood from clotting an anticoagulant (“blood thinner”) is added to the circuit to allow the blood to flow more easily. The standard anticoagulant used is heparin. Heparin is very effective in preventing the blood from clotting in the circuit. However, it may also affect the clotting of the blood in the patient’s body, resulting in increased risk of bleeding and potentially triggering an immune response. In some patients, for example those with trauma, or who has had recent surgery or who are bleeding, the complications seen with heparin may be particularly problematic.

An alternative to the use of heparin is to use dialysis fluids based on citrate for so-called “regional anticoagulation”. Regional anticoagulation refers to that the anti-clotting effect is only seen in the circuit. The citrate-based solution is added to the circuit before the filter and therefore does not enter the patient’s body. This means that the citrate solution is effective in preventing the blood from clotting in the circuit without increasing the risk of bleeding or other complications to the patient.

Citrate-based solutions for CRRT with RCA have been used for regional anticoagulation for more than 40 years. In published studies, more than 3250 patients have been treated with various citrate

solutions. In addition more than 30.000 patients are estimated to have been treated with products similar to Regiocit.

VI.2.3 Unknowns relating to treatment benefits

In published studies from North and South America, Europe, Australia and Asia, patients were aged from new-borns to elderly over 80 years of age. There is no evidence to suggest that results would be any different in other patient groups.

Regiocit can be used in adults and children. In children, Regiocit is indicated in all age groups provided that the equipment used is adapted to the weight of the child.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Citrate toxicity (citrate intoxication)	Based on published studies it is estimated that 1-10 patients out of 1000 will experience citrate toxicity. The risk is higher with concentrated citrate solutions and in liver impairment. It is expected to be lower with isotonic solutions such as Regiocit	Yes, by close monitoring of the patient's calcium levels during treatment
Acidosis (metabolic acidosis)	Based on published studies it is estimated that 1-10 patients out of 1000 may experience metabolic acidosis. The risk is increased in liver impairment. The acidosis is generally mild to moderate and reversible upon correction of treatment.	Yes, by routine metabolic monitoring followed by discontinuation of citrate infusion and adjustment of replacement fluids composition when required
Alkalosis (metabolic alkalosis)	Based on published studies it is estimated that 1-10 patients out of 100 treated with citrate-based solutions such as Regiocit will experience metabolic alkalosis. The alkalosis is generally mild to moderate and reversible upon correction of treatment. Patients who require high citrate infusion rate or who received large volumes of citrate containing blood are at increased risk	Yes, by reducing the blood flow rate (reducing the citrate infusion rate), or by increasing dialysate flow rate

Risk	What is known	Preventability
Low calcium levels in the blood (hypocalcaemia)	Based on published studies it is estimated that 1-10 patients in 1000 treated with citrate-based solutions will experience low calcium levels. The risk is increased in liver impairment. The low calcium levels are generally mild and easily corrected by infusion of calcium through a separate line	Yes, by close monitoring of the patient's ionised calcium levels
Hyponatraemia	Based on published studies and experience from similar marketed products it is estimated that 1-10 patients in 1000 will experience low sodium level when treated with citrate-based solutions. Any imbalance is generally mild and easily corrected by adjustment of treatment.	Yes, by close monitoring of the patient's sodium levels
Hypomagnesaemia	Based on published studies it is estimated that 1-10 patients in 1000 will experience low magnesium level when treated with citrate-based solutions. Any imbalance is generally mild and easily corrected by adjustment of treatment.	Yes, by close monitoring of the patient's magnesium levels

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Particle blocks (particle embolism)	Particle blocks may occur due to precipitations (formation of solid particles) in the solutions. This may occur if a combination of magnesium and phosphate, hydrogen carbonate or glucose is added directly into the citrate-based solution by the operator. It is prevented by ensuring that any solution used is free from particles before use

Important missing information

None

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Regiocit can be found in the website of your national health authority.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No post-authorisation studies are proposed.

VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes to the RMP over time

Version	Date	Safety Concerns	Comment
1.0	At time of authorisation	Identified risks: Citrate toxicity Metabolic alkalosis Metabolic acidosis Hypocalcaemia Electrolyte imbalance Potential Risks: Hypernatraemia Blood loss Hypovolaemia Infection Particle embolism	

Version	Date	Safety Concerns	Comment
2.0	At time of authorisation	Identified risks: Citrate intoxication Metabolic alkalosis Metabolic acidosis Hypocalcaemia Hyponatraemia Hypomagnesaemia Potential Risks: Particle embolism	Hyponatraemia and hypomagnesaemia are not newly identified risk. They were described as a group (Electrolyte imbalances) in version 1.0 Blood loss and hypovolaemia are related with the procedure rather than with the medicinal product itself and consequently removed as potential risks of the medicinal product. The potential risk infection applies for any drug – i.e. potential for contamination - it is not a risk associated specific to the drug product itself. Consequently it has been removed as potential risks of the medicinal product.