Agence française de sécurité sanitaire des produits de santé

Direction de l'Evaluation
des Médicaments et des Produits Biologiques

PUBLIC ASSESSMENT REPORT
Scientific Discussion

RINGER LACTATE MACOPHARMA,
Solution for infusion

Sodium chloride, potassium chloride,
calcium chloride dihydrate, sodium lactate 60%

FR/H/313/01/MR

Applicant: MacoPharma

Date of the PAR: August 2007

Information about the initial procedure:

Application type/Legal basis	*Well-established use application 10.1 (a)*
Active substance	*Sodium chloride, potassium chloride, calcium chloride dihydrate, sodium lactate 60%*
Pharmaceutical form	*Solution for infusion*
Strength	*For 1000ml:* *Sodium chloride 6g* *Potassium chloride 0,40g* *Calcium chloride dihydrate 0,27g* *Sodium lactate 60% 5,16g*
Applicant	*MacoPharma*
EU-procedure number	*FR/H/313/01/MR*
End of procedure	*22 January 2007*

1. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the French Health Products Safety Agency (Afssaps) has granted a marketing authorisation for Ringer Lactate MacoPharma, solution for infusion.

This medicinal product is indicated for:
- Restoration of extracellular fluid and electrolyte balances or replacement of extracellular fluid loss where isotonic concentrations of electrolytes are sufficient.
- Short term volume replacement (alone or in association with colloid) in case of hypovolemia or hypotension.
- Regulation or maintenance of metabolic acidosis balance and/or treatment of mild to moderate metabolic acidosis (except lactic acidosis).

A comprehensive description of the therapeutic indications and doses is given in the SPC.

This was a bibliographic application supported by detailed references to the published pharmacology, efficacy and safety of the product. No new preclinical or clinical studies were submitted, which is acceptable for a well-established use application.

2. QUALITY ASPECTS

2.1 Introduction

Ringer Lactate MacoPharma, solution for infusion is presented in flexible plastic bags of 250 ml, 500 ml and 1000 ml, made of PVC bags and non-PVC bags.
In total four different packaging systems are supplied; PVC bags and non-PVC bags, with or without infusion set. All the presentations are over-wrapped.

2.2 Drug substance

The four active substances, sodium chloride, potassium chloride, calcium chloride dihydrate and sodium lactate (solution 60% w/w) are controlled in accordance with the European Pharmacopoeia monographs in force. Additional tests are also performed: IR spectrophotometry, bacterial count and endotoxins according to Eur.Ph. <2.6.12, 2.6.14>.
The manufacturer of sodium lactate solution holds a certificate of suitability of the monograph.

Stability studies under ICH conditions have been conducted performed for each active substance stored in commercial packaging. The data provided are sufficient to confirm the retest period.

2.3 Medicinal product

Ringer Lactate MacoPharma, solution for infusion is formulated using drug substances and excipients (water for injection) described in the current Eur.Ph.
The drug product complies with Eur.Ph. monograph for solution for infusion and the physiochemical and biological properties of the Ringer Lactate solution comply with B.P. monograph. The pH range is 5.0-7.0.
The development is sufficiently described in accordance with the relevant European guidelines.
The manufacturing process has been sufficiently described and critical steps identified. The finished product is terminally sterilised using overkill conditions complying with the Eur.Ph. reference conditions. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.
The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.
Stability studies under ICH conditions have been performed. The data support the shelf life claimed in the SPC, 2 years with the following storage precaution "Do not store above 25°C and store in the original outer container".

3. NON-CLINICAL ASPECTS

3.1 Discussion on the non-clinical aspects

Ringer Lactate infusion solution is a product with a well-established use. The components of the MacoPharma Ringer Lactate formulation do exist throughout the body, and so, are generally regarded as safe.

No new preclinical, pharmacology, or pharmacokinetics studies were performed on this formulation. However in view of the extensive experience in patients with this formulation, there is no need to perform such studies.

The PVC bags and polyolefine bags of the MacoPharma Ringer Lactate solution do no present risk for humans. Concerning leachable substances which could migrate from the bags, except diethyl hexyl phthalate ester (DEHP) no plasticizer, antioxidant, adhesives or preservatives were identified in the solution, and there is no human risk from these products.
A safety assessment of DEHP was performed. It was concluded that there is little to no risk related to the exposure to the small amount of DEHP released from PVC IV bags.

4. CLINICAL ASPECTS

4.1 Introduction

Components of Ringer Lactate solution, namely sodium chloride, potassium chloride, calcium chloride dihydrate, and sodium lactate 60 % are physiologically present in the body. The product is a well-known preparation with well-established efficacy and safety profile in patients.

4.2 Discussion on the clinical aspects

Ringer Lactate has been used in clinical practice since Hartmann adapted Ringer's Solution in 1934. The product has been licensed in Europe for over 50 years as a crystalloid intravenous infusion for use in extracellular dehydration treatment, short term volume replacement, and regulation or maintenance of metabolic acidosis balance (excluding lactic acidosis).

Ringer Lactate MacoPharma was first approved in France in April 1989, and was also authorised in Belgium (1991), Germany (2000), Israel (2002) and Switzerland (2003).

Ringer Lactate solution for infusion is a fluid replacement, especially suitable for dehydration states. The role of anions and cations is predominant to restore normal osmotic conditions of the extracellular and intracellular fluids.

No new clinical studies were conducted, which is acceptable for this kind of product with more than 10 years of experience.

In terms of efficacy assessment, the issue was not whether compound sodium lactate is efficacious, but whether, it remains efficacious compared to alternative solutions and whether the safety profile remains acceptable.

The proven efficacy of Ringer Lactate in fluid rehydration has led The American College of Surgeons to recommend the use of Ringer Lactate solution as the initial fluid treatment of choice for the patients with hemorrhagic shock [Ho *et al*, J Trauma (2001)].

Evidence from the literature supports the use of Ringer Lactate to treat and prevent metabolic acidosis. Indeed, the use of balanced IV solutions can prevent the development of hyperchloremic metabolic acidosis and provide better gastric mucosal perfusion compared with saline-based fluids.

The potential safety issues may be related to the metabolism of the constituents i.e. sodium, potassium, calcium, chloride and lactate, and to the clinical condition of the patient. Overall, when contraindications and precautions for use are followed, Ringer lactate solution is safe, as shown in routine practice since the early days of clinical use.

The safety profile can be considered as well-established and no product-specific pharmacovigilance issues were identified which are not already covered adequately by the current SPC.

A potentially serious public health concern has been raised by one CMS during the procedure, considering that some SPC sections should be further clarified. In particular, the therapeutic indications in Section 4.1 were reworded in more precise terms and Section 4.2 was completed to mention the doses and infusion rate.

4.3 Pharmacokinetics

The pharmacological properties of the Ringer Lactate solution are related to the individual components of the preparation, namely sodium chloride, potassium chloride, calcium chloride dihydrate, sodium lactate and water, which are all present physiologically in the body.

The pharmacodynamic effects of Ringer lactate solutions are well known, due to a long-standing experience. Ringer lactate solution due to its intravenous route of administration makes the product 100% bioavailable. Ringer lactate solution is iso-osmolar to blood serum and it distributes mainly in the extracellular fluids. The metabolism of the solution is that of its constituents.

It was concluded that no further relevant information would be obtained from additional studies.

5. OVERALL DISCUSSION , BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ringer lactate solutions have been used since the early days of infusion therapy in clinical medicine.

Being one of the most used standard infusion solutions, its efficacy and safety has been proven by the worldwide clinical experience. The benefit/risk balance of the MacoPharma Ringer lactate solution was favourable, based on comprehensive literature data. No additional toxicological or clinical studies were deemed necessary for this application.

Comments from CMS have been received, requesting the implementation of information in SPC to be in agreement with the MRP-approved SPC from other procedures. Finally, all the CMS mutually recognised the marketing authorisation of Ringer Lactate MacoPharma, solution for infusion initially granted by the Afssaps.

The SPC, Patient Leaflet and packaging were presented according to the agreed template.