LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Hemosol B0

(lactic acid, calcium chloride, magnesium chloride, sodium chloride and sodium hydrogen carbonate)

SE/H/171/01/E01/MR

This module reflects the scientific discussion for the approval of Hemosol B0. The procedure was finalised at 2009-10-15. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Gambro Lundia AB has gained a marketing authorisation for Hemosol B0 solution for haemofiltration and haemodialysis. The active substances are lactic acid, calcium chloride, magnesium chloride, sodium chloride and sodium hydrogen carbonate, used as electrolytes in this substitution solution used in haemofiltration and dialysis solution in haemodialysis. The electrolyte ions are judged to contribute to the clinical efficacy and are therefore considered as active substances.

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Hemosol B0 is presented in the form of a solution for haemofiltration and haemodialysis containing a number of electrolytes all considered as active substances. The excipients are carbon dioxide as pH adjuster and water for injections used as solvent. The solution is filled in two different containers, a two-compartment PVC bag or a two-compartment peel-sealed polyolefin bag.

II.2 Drug Substance

All the drug substances are inorganic substances commonly used as excipients and they all have monographs in the Ph Eur.

Declarations from the manufacturers confirming that the manufacturing process used do not leave any impurities which are not adequately controlled in the current Ph Eur monographs are included in the dossier, or if necessary additional information have been provided in the dossier.

The drug substance specifications include relevant tests and limits. The analytical methods applied are performed according to the Ph Eur methods and no validation data is presented.

No stability studies have been performed with the drug substances. The Marketing Authorisation Holder has committed to introduce re-test periods for the drug substances, based on stability data, via a type II variation before the end of 2010.

II.3 Medicinal Product

Hemosol B0 solution for haemofiltration and haemodialysis is formulated using excipients described in the current Ph Eur. No components, reagents or raw material of animal origin are used during manufacturing of the drug product.

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

The manufacturing process has been sufficiently described and critical steps identified. 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 and data presented support the shelf life claimed in the SPC, when stored not below 4°C.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology/Pharmacokinetics/Toxicology

Pharmacological and toxicological studies with Hemosol B0 have not been performed. The omission of preclinical studies is justified by the clinical experience with solutions with similar composition as Hemosol B0 used for haemofiltration or haemodialysis. Furthermore, the composition of the reconstituted solution complies with the Ph. Eur. monographs on solutions for haemofiltration/haemodiafiltration and haemodialysis. The packaging materials meet the physico-chemical requirements stated in the international standards.

III.2 Ecotoxicity/environmental risk assessment

No information is provided on the solutions and is not considered necessary. The packaging materials are regarded as non-toxic and can be disposed as ordinary household refuse by controlled dumping, landfill or incineration in suitable furnaces.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical documentation provided consisted of an expert report and published data.

IV.2 Pharmacokinetics

No information was provided. However, SPC sections 4.5 and 4.9 were updated in August 2003. The changes included information concerning potential interactions with other medications due to electrolyte and/or acid-base imbalances and extended information concerning overdose.

IV.3 Pharmacodynamics

No product-specific information was provided. General referral was made to the well-known actions of the contained electrolytes and bicarbonate.

IV.4 Clinical efficacy

There is no detailed information from clinical studies performed with Hemosol B0. A number of submitted publications report experience with bicarbonate-buffered solutions in CRRT. The relative scarcity of clinical documentation specific to the use of bicarbonate-buffered replacement solutions in CRRT was regarded as acceptable in the light of the long-standing experience with bicarbonate-containing dialysis fluids. The buffer content of Hemosol B0 complies with the updated Ph. Eur. monographs on solutions for haemodialysis and haemofiltration/haemodiafiltration that has been implemented recently. Previously most of the haemofiltration solutions used for CRRT was lactate based solution, usually with a concentration of 40-45 mmol/l. As suggested by the submitted study by Kierdorf *et al.*, Hemosol B0 may be slightly less efficient than such solutions for achieving full control of acidosis during CRRT in some patients. Considering the frequent monitoring of acid-base status undertaken in ICU patients on CRRT, this is not considered a major problem.

IV.5 Clinical safety

The medical expediency of a two-compartment product like Hemosol B0 is specifically influenced by handling safety. Inadvertent administration of the electrolyte solution without prior bicarbonate addition, either parenteral, or for dialysis, would be deleterious to the patient. This was considered as a safety issue in the primary evaluation. However, currently the two components are packed in a two compartments PVC or polyolefin bag with the buffer solution (250 ml) in the smaller compartment and the electrolyte solution (4750 ml) in the larger compartment. The two compartments are separated by a frangible pin or a peel seal. The buffer

solution should be added to the electrolyte solution after breaking the frangible pin or the peel seal and before administration to the patient. This new compartment bag should diminish the risk of administration of the electrolyte solution without prior bicarbonate addition.

IV.6 Discussion on the clinical aspects

The relative scarcity of clinical documentation specific to the use of bicarbonate-buffered replacement solutions in CRRT was regarded as acceptable in the light of the long-standing experience with bicarbonate-containing dialysis fluids. The medical expediency of a two-component product like Hemosol B0 is specifically influenced by handling safety. The new compartment bag should diminish the risk of administration of the electrolyte solution without prior bicarbonate addition. Thus, from a clinical point of view, the benefit risk balance is considered as positive.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has been performed and is acceptable.

The risk/benefit ratio is considered positive and Hemosol B0 solution for haemofiltration and haemodialysis is recommended for approval.

Commitments were made by the applicant in relation to a minor change in the SPC, withdrawal of a drug substance manufacturer as well as introduction of re-test periods for the active substances. A type II variation covering the commitments will be applied for before the end of 2010.

VI. APPROVAL

Hemosol B0 solution for haemofiltration and haemodialysis, was nationally approved in Sweden in 1998 and via a mutual recognition procedure approved in the CMSs AT, BE, DE, DK, EL, ES, FI, FR, IE, NL, PT and UK in 1999.

The Repeat use Mutual recognition procedure for Hemosol B0 solution for haemofiltration and haemodialysis (CMSs BG, CY, CZ, EE, HU, IS, LT, LU, LV, MT, NO, PL, RO, SI and SK) was successfully finalised on 2009-10-15, the common renewal date will be 2014-10-15.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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