Public Assessment Report

Scientific discussion

Human Albumin "CSL Behring"
5% and 20% solution for infusion

Human albumin

DK/H/1508/001-002/E/002

This module reflects the scientific discussion for the approval of Human Albumin "CSL Behring". The procedure was finalised on 9 December 2009. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Human Albumin "CSL Behring" 5% and 20% solution for infusion, from CSL Behring GmbH was first authorised in Denmark on 9 July 2004 following the repeat use procedure AT/H/0123/001-002/E/001. Initially AT acted as RMS; however transfer of RMS from AT to DK was agreed in 2008.

The initial mutual recognition procedure was finalised positively on 30 October 2002 (AT/H/0123/001-003/MR). The 1st wave repeat use procedure was finalised positively on 24 February 2004 (AT/H/0123/001-002/E/001). Denmark was included via this repeat use procedure.

This report concerns the 2nd wave repeat use procedure initiated on 10 September 2009.
Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Human Albumin "CSL Behring" 5% and 20 % solution for infusion, from CSL Behring GmbH. The 2nd wave repeat use procedure was finalised on 9 December 2009. The product is indicated for restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated and use of a colloid is appropriate.

Human albumin belongs to the group of plasma substitutes and protein fractions. Human albumin 50g/l is mildly hypooncotic to normal plasma whereas human albumin 200 g/l has a hyperoncotic effect. The most important physiological functions of albumin results from its contribution to oncotic pressure of the blood and transport function. Albumin stabilises circulation blood volume and is a carrier of hormones, enzymes, medicinal product and toxins.

The present dossier has been updated to include all variations approved since finalisation of the 1st wave repeat use procedure (AT/H/0123/001-002/E/001).

The marketing authorisation is granted based on article 10a (well established use application) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Human Albumin "CSL Behring" 5% solution for infusion is a solution containing 50 g/l of total human plasma protein of which at least 96% is human albumin.
Human Albumin "CSL Behring" 5 % is mildly hypooncotic to normal plasma.

Human Albumin "CSL Behring" 20% solution for infusion is a solution containing 200 g/l of total human plasma protein of which at least 96% is human albumin.
Human Albumin "CSL Behring" 20% is hyperoncotic to normal plasma.

Human Albumin "CSL Behring" is a clear, slightly viscous liquid; it is almost colourless, yellow, amber or green.

Human Albumin "CSL Behring" 5% is provided in 100 ml, 250 ml and 500 ml infusion bottles, glass type II (Ph.Eur.). However, not all pack sizes may be marketed.
Human Albumin "CSL Behring" 20% is provided in 50 ml and 100 ml infusion bottles, glass type II (Ph.Eur.). However, not all pack sizes may be marketed.

The excipients are: sodium N-acetyltryptophanate; sodium caprylate; sodium chloride and water for injections.

Compliance with Good Manufacturing Practice

The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

II.2 Drug Substance

Human albumin 5% and 20% solution is manufactured from pools of human plasma, in compliance with the requirements of the Ph.Eur monograph Human Albumin Solution (01/2008:0255).

The starting material for human albumin 5% and 20% is covered by the centrally-authorised PMF EMEA/H/PMF/000001/04.

The manufacture of human albumin is based on the Kistler-Nitschmann modification of Cohn's cold ethanol fractionation. The product is virus inactivated by heat treatment in the final container (pasteurisation).

The manufacturing process consists of two modules: the "main fractionation" and "albumin bulk preparation".

Relevant in process controls are applied during the drug substance manufacturing process. All IPCs are performed according to relevant Ph.Eur. chapters where applicable.

The drug substance manufacturing process has been sufficiently validated. Results of the validation show that the approved manufacturing procedure ("main fractionation" and "albumin bulk preparation") consistently produces products that meet their specifications.

The drug substance specification includes the parameters: pH, sodium content, potassium content, total viable germ count and density. The analytical methods are in accordance with relevant Ph.Eur. chapters where applicable.

Human albumin 5% and 20% solution is manufactured from human plasma in a continuous manufacturing process. The drug substance human albumin is not isolated as intermediate; its characterisation occurs in the drug product. Additionally, the batch analyses and stability studies are only performed for the drug product.

II.3 Medicinal Product

The pharmaceutical development of the product has been described.

The drug product manufacturing process consists of the filling of albumin bulk solution into infusion bottles, followed by a pasteurisation step (60 ± 0.5°C for 10.5 ± 0.5 hours followed by an incubation period). After incubation all bottles are controlled to be free of turbidity and sedimentation.
Re-pasteurisation is performed in specific cases. It has been demonstrated that reprocessing (up to 4 times pasteurisation) does not adversely affect the quality of the product at release and during shelf life.

Comprehensive retrospective validation studies and additional validation studies have been performed documenting the validity of the different modules of the drug product manufacturing process: filling, pasteurisation and visual inspection.
The aseptic processing has been sufficiently validated through microbial challenge test of the sterile filter; media fill tests and container closure integrity test.

In general, the specifications for the drug product are set according to the requirements of the Ph. Eur. monograph Human Albumin Solution (01/2008:0255).

The analytical methods have been briefly described and sufficiently validated.
Batch analysis data of several batches produced is provided. The data are comparable and in accordance with specification thus indicating that the drug manufacturing process is robust.

Stability data is provided for all fill sizes of both strengths. All results are within specification and support the shelf life of 36 months with the storage conditions: Do not store above +25 °C. Do not freeze. Keep the infusion bottle in the outer carton in order to protect from light.

Virus safety
Studies have been performed in order to validate the capacity of the production process to inactivate/remove viruses. Generally, the design of these studies was according to the requirements of the Note for Guidance on Virus Validation Studies (CPMP/BWP/268/95). High overall reduction factors were obtained for all viruses tested.
Four different manufacturing steps contributed to virus clearance: three fractionation/filtration steps and one pasteurisation step. Pasteurization inactivated a wide variety of enveloped model viruses as well as the non-enveloped B19 virus with high efficiency to levels below detection.

A viral risk assessment has been performed according to CPMP/BWP/5180/03 showing that the residual risk per dose of final product can be considered negligible.

Based on the virus clearance studies performed, the viral safety of Human Albumin “CSL Behring” 5% and 20% solution for infusion is considered adequately documented.

III. NON-CLINICAL ASPECTS

The preclinical dossier is based on literature only and no pharmacological or toxicological studies have been performed with Human Albumin "CSL Behring". This is acceptable with respect to the wide and long-term use of human albumin in clinical practice.

No amendments have been made to dossier regarding non-clinical aspects since the 1st wave repeat use procedure (AT/H/0123/001-002/E/001) except for updating the dossier to eCTD.

IV. CLINICAL ASPECTS

IV.1 Introduction

This is an application based on well established use. No studies with Human Albumin "CSL Behring" have been submitted.

No amendments have been made to dossier regarding clinical aspects since the 1st wave repeat use procedure (AT/H/123/001-002/E/001) except for updating the dossier to eCTD.

IV.2 Risk management plan & Pharmacovigilance system

The safety profile of human albumin can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation.

The Pharmacovigilance system described fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the identification and notification of any potential risks occurring either in the Community or in a third country.

V. PRODUCT INFORMATION

SmPC and Package leaflet

The content of the SmPC and package leaflet approved during the repeat use procedure is in accordance with the core SPC for human albumin (CPMP/BPWG/2231/99 Rev. 2).

Readability test

The package leaflet 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 results hereof were submitted via a type II variation procedure DK/H/1508/001-003/II/004.The language used for the purpose of user testing the package leaflet was English. The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Human Albumin “CSL Behring” 5% and 20% solution for infusion has a proven physical-chemical and biological quality. Due to the wide and long-term use of human albumin in clinical practice, the product has an established favourable efficacy and safety profile.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC, package leaflet and labelling are in the agreed templates and the content of the SmPC and package leaflet approved during the repeat use procedure is in accordance with the core SPC for human albumin (CPMP/BPWG/2231/99 Rev. 2).

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that a marketing authorisation could be granted. The 2nd wave repeat use procedure was finalised on 9 December 2009.

The PSUR submission cycle is 3 years. The next PSUR will be submitted with a data lock point of 20 October 2009.

The date for the next renewal will be: 27 June 2012.

The following post-approval commitments have been made during the procedure:

- As the SPC, PL and labelling cannot be amended during this repeat use procedure the applicant has made a commitment to implement the changes via a type II variation within 6 month of finalisation of the repeat use procedure.

- Regarding the third strength 25% (DK/H/1508/003) the applicant will be updating the dossier in agreement with the amendments to the 5% and 20% strengths.

- The applicant commits to submittting a variation application introducing all updates which have been proposed in this repeat-use procedure as a response to Questions 39, 28, 29, 33, 34, 36 and 40. This variation application should be submitted within 6 months.