8 August 2012
EMEA/CHMP/329441/2005

Committee for Medicinal Products for Human Use (CHMP)

Consultation procedure Public Assessment Report (CPAR)

Consultation on an ancillary medicinal substance incorporated in a medical device

Medical device: Steen solution™

Ancillary medicinal substance: Human serum albumin

EMEA/H/D/000002

Applicant: Det Norske Veritas Certification A/S

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted

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Administrative information

Name of medical device:	Steen solution™
INN (or common name) of the ancillary medicinal substance:	Human serum albumin
Notified Body	Det Norske Veritas Certification A/S
Applicant for device approval	Vitrolife Sweden AB
Applied intended purpose of the device	For ex vivo evaluation of lungs intended for transplantation.
Intended purpose of the ancillary medicinal substance in the device:	The function of HAS is to create a colloid osmotic pressure similar to human blood.
Strength/Concentration and presentation of the ancillary medicinal substance(s) as part of the device(s):	7%, 70 g/l Liquid solution

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1. Background information on the procedure

1.1. *Submission of the dossier*

The applicant Det Norske Veritas Certification A/S submitted to the European Medicines Agency (EMEA) on 7 February 2005 an application for Consultation on Human serum albumin as ancillary medicinal substance used in a medical device Steen solution™, in accordance with the procedure falling within the scope of Directive 93/42/EEC, as amended.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Prof Ingemar Persson Co-Rapporteur: Dr Manfred Haase

1.2. *Steps taken for the assessment of the product*

- The application was received by the EMEA on 18 March 2005.
- The procedure started on 28 March 2005.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 June 2005. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 7 June 2005.
- During the meeting of 26 - 28 July 2005, the CHMP agreed on the consolidated List of Questions to be sent to the Notified Body. The final consolidated List of Questions was sent to the Notified Body on 1 August 2005.
- The Notified Body submitted the responses to the CHMP consolidated List of Questions on 12 August 2005.
- The Rapporteurs circulated the Joint Assessment Report on the Notified Body's responses to the List of Questions to all CHMP members on 9 September 2005.
- During the meeting of 11 – 13 October 2005, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion on the quality, safety and usefulness of Human Serum Albumin as ancillary medicinal substance used in Steen Solution on 13 October 2005. The Notified Body provided the letter of undertaking on the recommended measures to be fulfilled post-authorisation on 7 October 2005.

2. General conditions for the use of ancillary medicinal substances in medical devices

2.1 Manufacturers

Manufacturer of the active substance used as ancillary medicinal substance

Talecris Biotherapeutics
8368 US 70 West Clayton, North Carolina 27520, USA

Manufacturer responsible for import and batch release in the European Economic Area

Bayer Biologicals S.r.l.
Bellaria, 35, I-53010 Torri-Sovicille (SI), Italy

Manufacturer of the device

Vitrolife Sweden AB
Factorvägen 13, SE-434 37 Kingsbacka, Sweden

In accordance with Council Directive 93/42/EEC, as amended, a sample from each batch of bulk and/or finished product of the human blood derivative shall be tested by a State laboratory or a laboratory designated for that purpose by a Member State.

Recommended measures to the Notified Body

As discussed at CHMP, it would be recommended that the Notified Body request the following from the applicant for device approval:

Area1	Description	Due date2
Quality	The manufacturer of the active substance used as ancillary medicinal substance (Talecris) should commit to perform the planned stability study and to report any out of specification results to the Notified Body. The final study report should be submitted.	28/02/2007
Quality	Vitrolife should perform a stability study including 3 batches of Steen Solution 500 ml, produced with the Talecris Albumin (Human), 25% L/A, where the batches are produced at normal production intervals, i.e. every 4-6 months. Vitrolife should provide any out of specification results to the Notified Body during the study. An interim stability study report should be submitted to the Notified Body by November 1, 2006 and the final stability study report should be submitted by November 1, 2007.	01/11/2006 01/11/2007

1. Areas: Quality, Safety, Usefulness
2. Due date for the recommended measure or for the first interim report if a precise date cannot be committed to.

3. Scientific discussion

3.1. Introduction

The STEEN solution, intended for use in the evaluation of the suitability of human lungs ex vivo prior to lung transplantation, is classified as a medical device according to Council Directive (93/42/EEC). The solution incorporates human albumin as a medicinal substance with ancillary action. The Notified Body, Det Norske Veritas, is consulting the CHMP regarding the quality, safety and usefulness of the albumin component of the STEEN Solution according to Directive (2000/70/EC).

Human albumin is incorporated in Steen Solution in order to create a physical colloid osmotic pressure necessary to minimise damage to the lungs during the ex vivo assessment of functionality of isolated lungs after removal from the donor body prior to eventual transplantation.

The albumin used for this purpose is Human Albumin, low aluminium (L/A) 25% from Bayer. Human Albumin L/A 25 % is licensed in Germany and Greece under the name Plasbumin. Other strengths of Plasbumin (5%, 20%) are also approved in Italy and Spain. The final concentration of albumin in the STEEN solution is 7 g/l.

Human Albumin L/A is manufactured according to the Cohn-Oncley fractionation and in compliance with the PhEur. monograph “Human Albumin Solution”. The plasma used for the production of Human Albumin L/A is covered by Bayer’s Plasma Master File (PMF) which was recently assessed in the centralised PMF certification process and the certificate was issued in February, 2005.

3.2. Medicinal product before incorporation in the medical device

Introduction

Description

Human Albumin L/A 25% is a clear, slightly viscous, pale yellow to amber coloured solution. The active substance is human albumin. The albumin content in the product is not less than 96%.

Composition

Ingredient	Reference	50 ml amount	100 ml amount	Function
Protein1	EP	12.5 g	25 g	Active ingredient
Sodium caprylate	In-house			Stabiliser
N-acetyl-DL-tryptophan	EP			Stabiliser
Sodium2	In-house			Tonicity
Water for injections	EP			Solvent

1 NLT 96% of the content is albumin
2 represents sodium ion content from all sources incl. Sodium caprylate

Excipients

Sodium caprylate and N-acetyl-DL-tryptophan are used as excipients to stabilise and to reduce the formation of aggregates. The use of sodium caprylate to protect albumin solution was first published in 1944. The binding of N acetyl-DL-tryptophan to albumin and the stabilising capacity during pasteurisation was first published in 1958.

Container closure system

The container consists of glass vials. The stoppers are made of a halo butyl isoprene-blend elastomer. A flip-off seal is also used for sealing the vials.

Quality Aspects

Active Substance

The drug substance is defined as a sterile bulk material prior to sterile filling.

- **General Information**

Nomenclature

The Ph Eur. name of the active ingredient is Human Albumin Solution (Albumini Humani Solutio).

Structural Formula

A short description of the albumin molecule has been provided. Albumin consists of one single polypeptide chain of 585 amino acides cross linked by 17 disulfide bridges. The protein has a high degree of alpha helical structures and is folded into three domains. Each cylinder like domain has a hydrophobic inner space where hydrophobic substances such as fatty acids can bind. The outer surface of the molecule is mainly polar.

General Properties

The active substance human albumin is derived from human plasma.

- **Manufacture**

Manufacturer(s)

Talecris is responsible for the production of the drug substance fraction V, the aseptic filling and analytical testing. Bayer Biologicals in Italy is responsible for final product release testing, final product packaging and batch release.

Definition of a batch

The fractionation volume of a plasma pool is about 3600 l and yields approximately 270 kg paste V. A purification batch is defined as the final albumin bulk derived from approximately 588 kg fraction V paste. The final bulk is a sterile solution and contains the appropriate stabilizers and electrolytes. A typical bulk size is about 800 kg.

Description of Manufacturing Process and Process Controls

The manufacturing of the drug substance has been adequately described and optional steps have been clearly indicated. The manufacture of the sterile bulk is basically performed in two separate sequential processes: Cohn-Oncley fractionation followed by further purification steps. The fractionation is a well-established method and consists of steps from plasma pooling to final Fraction V step. A series of cold alcohol precipitation steps, in which differences in pH, temperature and alcohol concentration are used, to separate the different protein fractions in plasma.

The purification consists of steps from suspension of fraction V paste to the sterile bulk and follows the usual procedures in albumin purification with an exception: the manufacturer uses an additional acetone extraction step.

Control of Materials

The Plasma Master File (PMF) covering the human plasma for fractionation used as starting material for the drug substance has already been approved in the centralised PMF certification procedure. Only plasma certified by the centrally approved PMF is used for the production of human albumin incoporated in the STEEN solution.

Traceability is a key issue when plasma is used in the production of intermediates and drug products. There is a link, through the manufacturer of the Human Albumin to post-collection information on the donors and to post-marketing data on the albumin and its starting material (plasma pool) until the expiry date of the medicinal device (STEEN Solution) containing the albumin. The expiry date of the albumin is not earlier than that of the medical device.

All relevant contracts between the manufacturer of albumin and the manufacturer of the medical device regarding traceability will be updated accordingly. This work is already in progress and the documentation regarding manufacturing sites was updated in the dossier.

Control of Critical Steps and Intermediates

The control of the manufacturing process is deemed acceptable and relevant in-process controls are in place.

Microbiological quality is monitored to ensure the necessary controls are in place to minimize potential product contamination. Information on all processing steps/conditions, the specification limits, reaction times, viral removal capacity and options for process-interruptions or storage time of intermediates are sufficiently provided.

Process Validation

The manufacturing process has been sufficiently validated and consistency of the production process has been adequately demonstrated. At least three qualification batches were used for the validation of the fractionation and purification steps of the process.

Critical parameters, operating parameters and intermediate testing results were evaluated to ensure consistency of each production step and that the final output of each system met the pre-established acceptance criteria. The acceptance criteria have been set using results from process characterisation, small-scale studies and/or historical process data.

In addition, the applicant presented data from process characterisation studies on the fractionation process and the purification process.
The first study covered the fractionation process from pooled plasma to fraction V paste.

Manufacturing Process Development

The manufacturing process is based on the Cohn-Oncely fractionation process first established in 1940s and later modified in 1950s including the addition of acetone drying. In the 1980s, diafiltration/ultra filtration was introduced to reduce sodium citrate and aluminium levels in the albumin solution. The composition of Albumin L/A 25% is formulated to comply with the PhEur. monograph “Human Albumin Solution”.

Specification

Appropriate specifications for the drug substance were set and justified

Analytical methods

The protein composition of the bulk is tested using an in-house method sufficiently described and validated.

Batch analysis

Data from three batches of drug substance were provided. All results complied with the set specification.

Container closure system

Stainless steel tanks with varying size are used for storing final bulk product at 5 °C in a class C area. The tanks are kept under positive air pressure and each tank is sterilised before use.

Stability

The stability studies presented for the sterilised bulk are acceptable and the suggested storage time is well justified.

Based on the submitted documentation a shelf life was considered acceptablefor the active substance and the intermediates, because the company committed to perform the planned post approval stability study and to report any out of specification results to the Notified Body.

Drug product

Pharmaceutical Development

The process development started in 1940 as E .J. Cohn developed a method of plasma fractionation to obtain human albumin. In the meantime, changing the ethanol concentration, the introduction of acetone washing, using dia- and ultrafiltration for improved cleaning, the introduction of pasteurisation and the addition of stabilisers modified the process.

Most of the description of pharmaceutical development is based on literature data since the Cohn-Oncely process is a well-established process. The excipients used are also well known and it is therefore acceptable that the applicant refers to the literature.

- **Manufacture of the Product**

Description of the manufacturing process and in-process controls

Production of the drug product consists of aseptic filling into final container, pasteurisation and incubation of final container after which the vials are stored. A flow chart of the process has been provided.

Re-processing can only be allowed to correct potential compromise in bulk sterility due to technical failure. Re-filtration of the final bulk that fails the test for sterility is not allowed.

Descriptions of the primary and secondary packaging have also been provided.

Control of critical steps and intermediates

The sterility is tested. The temperature is monitored in the pasteurisation step as well as in the incubation of the final container after the pasteurisation.

Control of excipients

Specifications for N-acetyl-DL-tryptophan and sodium caprylate in the finished product were provided. The specification for N-acetyl-DL-tryptophan complies with Ph. Eur. The specification for sodium caprylate has been tightened to comply with the Ph. Eur.

- **Product Specification**

Methods used for the release of the drug product are either Ph. Eur methods or equivalence to Ph. Eur methods has been demonstrated. Validation reports were provided for test methods, which are not performed according to the Ph. Eur. methods or for which no compendia method exists.

The specifications are based on on the requirements in the Ph. Eur. monograph for Human Albumin Solutions.

Container Closure system

The container consists of bottles of glass Halo butyl isoprene rubber blend stoppers are used as closure. Both bottles and stoppers meet the requirements of the PhEur. An crimp cap is also used to seal the stoppers.

- **Stability of the Product**

The data presented from an ongoing stability study support the proposed shelf life of 3 years at 25°C for the drug product. Since real time data is available for up to 42 months for four batches, the absence of accelerated data is acceptable.

Results from a study with 4 batches investigating stability during shipment supported a maximum allowable temperature excursion.

Facilities and Equipment

The applicant has provided description of facilities and equipment.

Adventitious Agents Safety Evaluation

Risk of contamination with animal or human TSE

Animal TSE

No materials of bovine or other TSE-susceptible animal species are used at production. Media Fills used for qualification comply with with Guideline EMEA/410/rev02.

Human TSE

The Albumin 25% is produced from human plasma in the USA. Donors are excluded with respect to (v)CJD risk according to US-regulations. The exclusion criteria have been described in the Plasma Master File (PMF) and were considered adequate and in line with Position Statement CPMP/BWP/2879/02. Intermediates of other suppliers are not used for production of the drug product.

The manufacturing process was investigated on its capacity to remove TSE agents. These investigational studies provide evidence that significant removal of prions can be expected from the manufacturing process.

Adventitious Viruses

The drug product, Albumin 25%, is produced from human plasma (USA) by the established Cold Ethanol Fractionation followed by pasteurisation according to Ph. Eur. Several steps of the production process were extensively validated for their virus inactivation/removing capacity including robustness studies. Enveloped viruses are effectively inactivated. Non-enveloped viruses have been demonstrated to be removed successively.

The virus safety of albumin 25% has been adequately demonstrated.

Discussion on chemical, pharmaceutical and biological aspects

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines and PhEur monograph for human albumin. The information provided in the application showed a consistent batch-to-batch production of Albumin 25% achieving an adequate quality for the drug substance and the drug product. The manufacturing process of the drug substance and drug product were described and validated in sufficient detail. The quality of the drug product is controlled by adequate test methods and specifications.

No materials of bovine or other TSE-susceptible animal species are used in production. The Albumin 25% is produced from human plasma. Donors are excluded with respect to (v)CJD risk according to US-regulations. In addition, investigational studies provided evidence that significant removal of prions can be expected from the manufacturing process.

The Plasma Master File (PMF) covering the human plasma for fractionation used as starting material for the drug substance is certified (EMEA/H/PMF/000004/04).

The capacity and robustness of the manufacturing process to inactivate and remove viruses has sufficiently been investigated and, in summary, the virus safety of Albumin 25% has adequately been demonstrated.

3.3. Medicinal product in the context of its use in the medical device

Introduction

Human serum albumin (HSA) is included in the formulation of STEEN solution in order to provide a biocompatible solution and to provide a physiological colloid osmotic pressure. The quality, safety and usefulness of albumin in the Steen Solution have been evaluated.

Quality, Safety and Usefulness

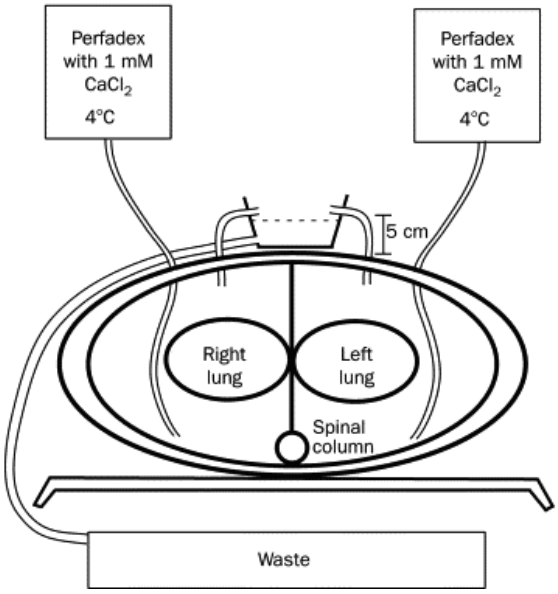
- **General Information**

The STEEN solution is intended for use in the evaluation of the suitability of human lungs ex vivo prior to lung transplantation. Below is a short outline of the current standard practice for lung evaluation and for the intended procedure under review by the Notified Body.

Current standard practice in brain-dead donors.

The normal starting point is a ventilated brain-dead patient whose relatives have given their approval of donation of the organ. Ventilation at different O2 concentrations with measurements of the corresponding oxygen partial pressure at the arterial side are used for a functional evaluation of the lungs in situ. The donor is also assessed for other diseases.

Lung evaluation in non-heart beating donors

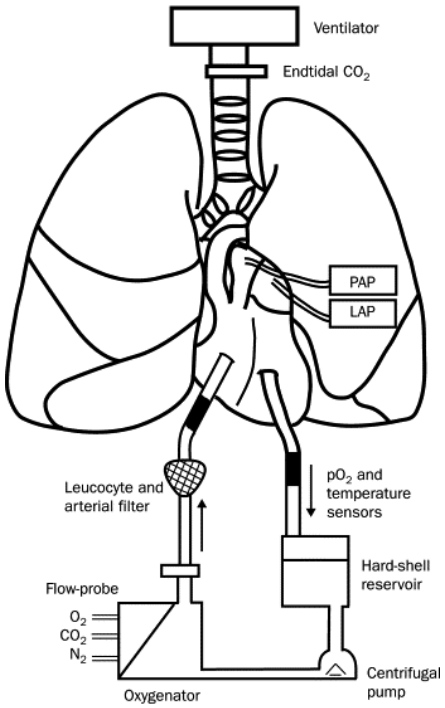


The starting point is a donor that has been non-heart beating for less than 30 minutes and the approval for donation has been received from the relatives. In preparation of topical cooling, a cannula is introduced in situ in the lowest space between the pleura and the lung of the donor (see figure at right). The cannula is connected to an IV bag with a buffered, cool (about 8o C) Perfadex® solution at a certain height above the highest part of the lung. the drainage is achieved via a cannula placed at the highest positioned part of the space between the pleura and the lung. The drainage is collected in a plastic bag.

When the temperature in trachea and the drainage is below 12o C, the cooling is deemed sufficient. The topical cooling is then discontinued and all the cannulas and external equipment are removed. After this is done, the relatives can stay with the donor's body for a maximum of two hours. After the relatives have left, the lung is perfused with Perfadex®, with the addition of buffer, calcium, heparin and nitroglycerine. The perfusion is made via the pulmonary artery through the capillary bed, pulmonary vein and finally the drainage is at the left atrium. The result of the perfusion is that all blood is drained out of the blood vessels and the capillary bed. The pulmonary package is then removed from the body, placed in a container filled with cold Perfadex® and transported to the recipient hospital.

Evaluation of the lungs ex vivo

At the recipient hospital, the lung package is connected to an ex vivo circulation with a lung evaluation solution. The circulation is as follows: pulmonary artery, capillary bed, pulmonary vein, left atrium, blood reservoir, roller pump, deoxygenator and, to close the circuit, a return cannula to the pulmonary artery (see figure at right). The circulating solution is created to function as artificial blood and is able to transport gases (15% erythrocytes) ; at the same time the solution, by the addition of albumin, should prevent fluid retention (oedema) within the lung tissue. Dextran 40 is claimed to cover the leucocytes and to prevent endothelial damage mediated by activated leucocytes. The concentrations of the added electrolytes are also chosen to avoid endothelial damage.



The deoxygenator is fed with N2 and CO2 to obtain a lowered defined PO2 pressure and a higher defined PCO2 pressure of the solution after the passage. The pressures are monitored with a sensor placed after the oxygenator. The solution perfuses the lungs which are simultaneously ventilated with 50% O2.

The total liquid volume is monitored in the blood reservoir. A reduced level reflects that the alveoli have become permeable and the lungs become oedematous. This may be a contraindication for transplantation.

The PaCO2 as measured next to the left atrium is compared to the end-tidal PCO2 in the expired air and the relation should be lower than 1 as this criterion is claimed to indicate absence of major embolia and thromboses. Another criterion for approval of the lungs is that the oxygenation is adequate. Furthermore by adding NO at different concentrations in the inhaled gas, the relationship between the NO-concentration and pulmonary vascular resistance can be studied. This relationship is claimed to reflect endothelial function.

The ex vivo evaluation also permits possibilities for treatment and re-conditioning of the lung (e.g. antibiotics) as well as diagnostic procedures (e.g. visual inspection, X-ray).

Qualitative and quantitative particulars of the constituents

The composition of the Steen Solution is as follows:

Ingredient
Dextran-40
Sodium chloride
Glucose
Potassium chloride
Sodium dihydrogen phosphate
Calcium chloride dehydrate
Magnesium chloride
Human serum albumin
Sodium hydrogen carbonate
Sodium hydroxide
Water for injection

- **Description of method of manufacture**

A description of method of manufacture for the Steen Solution with regard to the incorporation of the human albumin was provided including batch size and in-process controls.

The Notified Body performed an audit at Vitrolife in January 2005. Vitrolife has a Quality Management System in conformity with ISO 13485: 1996. The certificates were provided.

- **Controls of starting materials**

Albumin 25% is in compliance with the shelf life specification for the drug product. In accordance with Council Directive 93/42/EEC, as amended, a sample from each batch of bulk and/or finished product of the human blood derivative shall be tested by a State laboratory or a laboratory designated for that purpose by a Member State.

- **Control tests carried out at intermediate stages of the manufacturing process of the medical device**

Not applicable

- **Control tests on finished product**

The test parameters and specifications for the medical device were submitted.

- **Stability**

Based on the data provided a shelf-life of 12 month at 2 to 8°C is recommended for Albumin 25% incorporated in Steen Solution. In addition, 9 months data from an ongoing stability study with 3 batches of 500 ml Steen Solution were provided and Vitrolife committed to continue the study and to report any out of specification results to the Notified Body.

The medical device manufacturer confirmed that the expiry date of the albumin is not earlier than that of the medical device.

Other compatibility issues of the albumin incorporated into the Steen Solution and used under ex vivo conditions, such as compatibility with erythrocytes and the lung, are not within the scope of the EMEA consultation procedure.

- **Toxicity**

Cross- reference is made to the section “Local tolerance” (see below).

- **Reproductive function**

HSA is a well-known substance used already since the forties as a blood substitute to restore and maintain the oncotic pressure in the circulation. The intended function of HSA in STEEN Solution is the same in the pulmonary extracorporeal circulation during the evaluation performed ex vivo.

With reference to these facts and to the fact that the product is used ex vivo, the Applicant has not included any information regarding this section.

- **Embryo/foetal and perinatal toxicity**

The applicant has not included any information regarding this section; the justification provided is identical to the justification provided in section “Reproductive function” (see above).

- **Mutagenic potential**

The applicant has not included any information regarding this section; the justification provided is identical to the justification provided in section “Reproductive function” (see above).

- **Carcinogenic potential**

The applicant has not included any information regarding this section; the justification provided is identical to the justification provided in section “Reproductive function” (see above).

- **Pharmacodynamics**

The intended action of the inclusion of human serum albumin in the STEEN Solution is to control the colloid osmotic pressure in the device, to make it similar to that in human blood, 25 mmHg.

The concentration of HSA in blood is 45 g/L and is at that concentration responsible for about 70% of the colloid osmotic pressure. Since all other colloid osmotic components of the serum (gamma globulin, other proteins) are absent, the HSA concentration has to be increased to 64 g/L.

A further increase of the HSA concentration is required to compensate for the final dilution by erythrocyte concentrate, made at the clinic. This results in 64 g/L x 1.07 = 69 g/L. The addition of Dextran 40 at low concentration is judged to only marginally contribute to the oncotic pressure.

- **Pharmacokinetics**

The applicant has not included any information regarding this section; the justification provided is identical to the justification provided in section “Reproductive function” (see above).

- **Local tolerance**

The biocompatibility and safety of STEEN Solution was verified in 5 test systems with an identical lot of the medical device. The studies were selected using the ISO 10993: Biological evaluation of medical devices part 1: Evaluation and testing.

The following studies where performed:

1. Cytotoxicity study using the ISO agarose overlay method in mouse fibroblast cell cultures.

2. ISO modified intracutaneous study of rabbits.

3. Acute systemic toxicity study following IV dose range findings/limit dose study in the mouse.

4. Murine local lymph node assay by topically dosing the dorsum of the mouse ear.

5. In vitro haemolysis study of diluted rabbit blood.

6. White blood cell morphology study in vitro of anticoagulated whole canine blood.

7. In vitro Lee-White clotting time study of canine blood.

The results show that STEEN Solution is biologically safe and biocompatible.

- **Clinical documentation**

Overview of Preclinical and Clinical studies performed with Steen solution

The preclinical and clinical studies performed with Steen solution are summarised below. A formal assessment of these studies with regards to the medical device is beyond the scope of the CHMP assessment report. However, to some extent the results are considered to contribute to the evaluation of the potential “usefulness” of the HSA component for its intended purpose. Therefore a summary of the preclinical and clinical studies is provided below.

Tabulated summary

Study	Design	Study model/n	Study objective
1	Lung evaluation *ex vivo* with four different types of extra cellular solutions in fresh lungs for three hours of closed lung perfusion.	Pig/16	Establish appropriate concentration of HSA
2	Closed lung evaluation *ex vivo* with different haematocrit levels of the STEEN solution	Pig/6	Establish appropriate haematocrit level
3	Lung evaluation *ex vivo* with STEEN solution. Fresh lungs compared with lungs preserved 36 hours with Perfadex®.	Pig/12	Feasibility of lung assessment after 36 hours of storage in Perfadex®
4	Transplantation of lungs from non heart-beating donors after functional assessment *ex vivo*.	Pig/12	Feasibility of lung assessment after topical cooling of NHB donor lungs
5	Pre-clinical testing of two non heart-beating lung donation protocols in pigs	Pig/8	Feasibility of *ex vivo* lung assessment after eiher NHB or

			HB donor lungs
6	Clinical report-non heart-beating lung donation. Lung evaluation *ex vivo* with STEEN solution. Clinical experiences.	Human/6	Summary of clinical experience of *ex vivo* lung assessment at Lund's University hospital
7	Transplantation of lungs from a non heart-beating donor	Human/1	Case study of transplanted lung after *ex vivo* assessment
8	*Ex vivo* reperfusion of human lungs declined for transplantation	Human/20	Feasibility study of *ex vivo* lung assessment at Katholieke Universiteit Leuven
9	Lung evaluation of non-acceptable donors.	Human/6	Feasibility study of *ex vivo* lung assessment at Sahlgrenska University Hospital

Study 1: Preclinical report-lung evaluation ex vivo with four different types of extra-cellular solutions in fresh lungs for three hours of closed lung perfusion

The study was performed using 4 groups of of pigs to determine an appropriate composition of the priming solution. Closed lung perfusion was performed in vivo with different priming solution composition for each group (Perfadex®, Krebs solution, Krebs solution with 3.5% albumin and Krebs solution with 7% albumin). The lungs of the animals were evaluated ex vivo immediately after harvesting.

The use of the first three solutions mentioned above all resulted in pulmonary weight increases and in the case of Perfadex® use pronounced pulmonary oedema.

The use of Krebs solution with 7% albumin resulted in a stable lung weight during three hours and was judged to be the most suitable formulation considering weight stability and the risk for pulmonary oedema. This formulation (albumin concentration 69 g/L), with the addition of Dextran 40 in a concentration of 5 g/L, was used in all the following studies.

Study 2: Preclinical report – closed lung evaluation ex vivo and different hematocrit level with STEEN solution

The study was performed with 6 pigs and different concentrations of autologous red blood cells (hematocrit 15 to 30%) were evaluated during 5 hours of lung perfusion. The lowest pulmonary vascular resistance and pulmonary artery pressure was obtained with a haematocrit of 15%.

Study 3: Preclinical report – Lung evaluation ex vivo with STEEN solution. Fresh lungs and after 36 hours of lung preservation with Perfadex®

Two groups of pigs were used, the lungs from the control group (n=6) were assessed ex vivo immediately after removal from the donor animal. The lungs from the test group (n=6) were assessed 36 hours after removal. The lungs from the test animals were preserved in the Perfadex® solution during the 36 hour period of cold ischemia.

The ex vivo lung assessment performed with the STEEN solution showed that the lungs stored for a cold ischaemic period of 36 hours seemed to function as well as the freshly removed lungs (gas exchange function, pulmonary vascular resistance, arterial and venous pH etc.).

After the ex vivo evaluation of the 36 hours Perfadex® preserved lungs, the left lung was transplanted into a recipient animal. Following the implantation, a right pulmectomy was performed to make the recipient animal totally dependent on the transplanted lung. Lung function was evaluated 24 hours after the transplantation and the results were in good agreement with the ex vivo evaluation results.

Study 4: Preclinical study: Transplantation of lungs from non-heart beating donors after functional assessment ex vivo. Ann Thorac Surg 2003;76:244-52

The study was performed in 12 pigs. After induction of ventricular fibrillation and after a warm ischaemic time of 65 minutes the lungs were topically cooled and then the lungs were removed and assessed ex vivo in a perfusion circuit with the STEEN solution. Finally the left lungs weree transplanted into recipient animals followed by a right pulmectomy leaving the animals totally dependant on the transplanted lung. Normal blood gas values and vascular resistance were retained during the 24 hour observation period after the transplantation. The results showed that lung transplantation can be performed successfully following topical cooling and six hours of ischaemic storage in combination with ex vivo assessment.

Study 5: Preclinical testing of two non-heart beating lung donation protocols in pigs

The study was performed in pigs. A normal heart beating donation procedure was performed in the "flush" group (n=4), i.e. 10 minutes no touch after the heart stopped beating, antegrade flushing followed by retrograde flushing, 5 hours of cold ischemia and finally ex vivo assessment using the STEEN solution. A non-heart beating donation procedure was performed in the "topical" group, i.e. 10 minutes no touch after the heart stopped beating, another 50 minutes of warm ischemia, 5 hours of cold ischemia and finally ex vivo assessment using the STEEN solution.

The results were interpreted by the investigators to support the conclusion that the assessment system using the STEEN solution is efficient in determining the physiological status of non-heart beating donor lungs as well as traditional heart beating donor lungs. The results also suggested that the ex vivo perfusion system can offer extended ischemia times and facilitate treatment of suboptimal lungs before transplantation.

Study 6: Clinical report – Non-heart beating lung donation. Lung evaluation ex vivo with STEEN solution. clinical experiences.

The report describes the evaluation of six non-heart beating donors. In five of the six cases cooling was initiated, in the sixth a donation card was found expressing a negative will for donation. Out of the five donors two were excluded, one because of chronic bronchitis and the other because of inadequate cooling of the lungs due to pleural adherences. Two of the donor lungs that were evaluated ex vivo passed the test and were declared suitable for transplantation, but one of these donors was rejected because of hepatitis C.

The lungs from the other accepted donor were transplanted, with good lung function in vivo up to five months after transplantation. The transplanted case was described in detail in study 7.

Study 7: Transplantation of lungs from a non-heart beating donor, Lancet 2001; 357:825-29

The transplanted case mentioned in study 6 is reported in this article and a description of the procedure and the ex vivo assessment is provided. An editorial commenting the study appears in the same issue of the Lancet.

Study 8: Ex vivo reperfusion of human lungs declined for transplantation; a novel approach to alleviate donor organ shortage? Presented at the 11th annual meeting of the European surgical association, 2004.

The article summarises the ex vivo evaluation of 20 paired human lungs from multi-organ donors declined for primary transplantation by Eurotransplant as well as the local hospital after traditional evaluation. The results showed that the assessment system with STEEN solution is efficient in determining the physiological status of human lungs. The results also suggested, according to the investigators, that the ex vivo perfusion system can offer extended ischemia times and facilitate resuscitation of lungs with impaired function before transplantation.

Study 9: Lung evaluation of non-acceptable donors

The applicant submitted a short summary of the experience at the Gothenburg University where six pairs of lungs, which had been declined for transplantation, were evaluated ex vivo. The assessments were made twice, the first time after 8 hours of cold ischaemia and the second after another 24 hours of topical ECMO (extracorporeal membrane oxygenation). The study indicated a lung function improvement during the procedure since the PO2 increased for all lungs between the first and second assessment.

- **Labelling**

The applicant has enclosed the Instructions for Use.

Discussion on Quality, Safety and Usefulness

Human serum albumin (HSA) is included as ancillary medicinal substance in the formulation of STEEN solution in order to provide a biocompatible solution and to provide a physiological colloid osmotic pressure of approximately 25 mmHg. The user adds erythrocytes from the local blood bank up to a haematocrit of 15%.

Quality

The ancillary medicinal substance, Human Albumin L/A 25% fulfils the requirements of the PhEur. monograph for Human Albumin Solutions and the approved shelf life specifications. The albumin is not subjected to any modifications before being incorporated into the medical device. The STEEN solution is basically an isotonic solution with a pH of 7.4. The manufacturing process of STEEN Solution consists, in summary, of mixing the different ingredients followed by sterile filtration and filling into PTEG bottles. From the documentation provided it could be considered that the manufacturing process of the Steen Solution does not modify the human albumin after incorporation.

The stability of the albumin in the Steen Solution has been evaluated. Other compatibility issues of the albumin incorporated into the Steen Solution and used under ex vivo conditions, such as compatibility with erythrocytes and the lung, are not within the scope of the EMEA consultation procedure.

Safety and Usefulness

The non-clinical aspects of human albumin in the context of its use in the device are identical with the medical product before incorporation.

The local tolerance and biocompatibility of the medical device was investigated in 7 studies according to ISO 10993: Biological evaluation of medical devices part 1. The results show that STEEN Solution is biologically safe and biocompatible. The albumin used in the biocompatibility studies is HSA from Baxter, batch no #2837X413AA. Although it would have been preferable if HSA from Bayer had been used in the biocompatibility studies, assuming that the HSA from Baxter has been produced in accordance with the PhEur. monograph for human albumin solution, no major impact on the results of these studies is expected. Therefore the use of HSA from Baxter instead of HSA from Bayer in the lot of STEEN solution used in the biocompatibility studies can be accepted.

The justification provided by the applicant (i.e. use of albumin since more than 60 years and ex vivo use of Steen solution) for not including information regarding reproductive function, embryo/foetal and perinatal toxicity, carcinogenic potential, mutagenic potential and pharmacokinetics is acceptable to CHMP.

Albumin has been used extensively clinically since decades as a colloid for the restoration and maintenance of circulating blood volume in cases of intravascular volume deficiency. The most

important physiological function of albumin results from its contribution to the oncotic pressure of the blood. Furthermore, albumin functions as carrier of different endogenous and exogenous substances (e.g. hormones, medicinal products). HSA is included in the formulation in order to provide a biocompatible solution and to provide a physiological colloid osmotic pressure of approximately 25 mmHg. Solutions lacking HSA or with a lower HSA concentration induce pulmonary weight increase (oedema) during the ex vivo evaluation.

In summary, the concept to add an adequate amount of albumin to the solution for perfusion of the extracorporeal circuit can be considered as a useful method to provide a sufficient oncotic pressure. The choice of albumin rather than artificial colloids is reasonable considering the aim to compose a biocompatible solution.

Albumin produced with modern fractionation and manufacturing techniques has a reassuring safety record. The extensive long-standing clinical experience with albumin solutions and with medicinal products containing albumin as a constituent should be taken into account. Provided that the albumin is produced according to current regulatory standards, the risk for transmission of infective agents via albumin appears negligible. The lack of suitable organs contributes considerably to the severe prognosis in these patients. Possibly the proposed procedure for the evaluation of lungs ex vivo may allow an increase of the number of organs available for transplantation in the future.

Provided that the recommended measures listed in section 2.1 are accepted by the Notified Body, the claim for safety and usefulness of albumin as a component of the STEEN solution is accepted by the CHMP.

3.4 Overall conclusions and recommendation

Quality

The ancillary medicinal substance, Human Albumin L/A 25% fulfils the requirements of the PhEur. monograph for Human Albumin Solutions. The documentation on the manufacture of the albumin showed a consistent batch-to-batch production and an adequate quality. The quality and safety of the human plasma for fractionation used as starting material is certified in the centralised PMF certification procedure (EMEA/H/PMF/000004/04). TSE and virus safety of Albumin 25% have adequately been demonstrated.

The human albumin is not subjected to any modifications before being incorporated into the medical device. From the documentation on the incorporation of the albumin in the medical device it is concluded that the manufacturing process of the Steen Solution does not modify the human albumin after incorporation.

The stability of the human albumin in the Steen Solution has been evaluated. Other compatibility issues of the albumin incorporated into the Steen Solution and used under ex vivo conditions, such as compatibility with erythrocytes and the lung, are not within the scope of the EMEA consultation procedure.

Safety

Albumin produced with modern fractionation and manufacturing techniques has a reassuring safety record. The extensive long-standing clinical experience with albumin solutions and with medicinal products containing albumin as a constituent should be taken into account. Provided that the albumin

is produced according to current regulatory standards, the risk for transmission of infective agents via albumin is considered negligible.

Usefulness

Albumin has been used extensively clinically since decades as a colloid for the restoration and maintenance of circulating blood volume in cases of intravascular volume deficiency. The most important physiological function of albumin results from its contribution to the oncotic pressure of the blood. Furthermore, albumin functions as carrier of different endogenous and exogenous substances (e.g. hormones, medicinal products).

In summary, the concept to add an adequate amount of albumin to the solution for perfusion of the extracorporeal circuit can be considered as a useful method to provide a sufficient oncotic pressure. The choice of albumin rather than artificial colloids seems reasonable considering the aim to compose a biocompatible solution.

The lack of suitable organs contributes considerably to the severe prognosis in these patients. Possibly the proposed procedure for the evaluation of lungs ex vivo may allow an increase of the number of organs available for transplantation in the future.

Recommendation

Based on the CHMP review of data submitted, the CHMP considered by consensus that the quality, safety and usefulness of Human serum albumin used as ancillary medicinal substance in the Steen solution was favourable and therefore granted a positive opinion in the consultation procedure, provided that the recommended measures listed in section 2.1 are accepted by the Notified Body.