### Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lay summary</td>
<td>P2</td>
</tr>
<tr>
<td>Scientific discussion</td>
<td>P3</td>
</tr>
<tr>
<td>Steps taken for assessment</td>
<td>P14</td>
</tr>
<tr>
<td>Steps taken after assessment</td>
<td>P15</td>
</tr>
<tr>
<td>Summary of product characteristics</td>
<td>P16</td>
</tr>
<tr>
<td>Product information leaflet</td>
<td>P24</td>
</tr>
<tr>
<td>Labelling</td>
<td>P29</td>
</tr>
</tbody>
</table>
Human Albumin 20 g/l Solution for Infusion

(Human Albumin)

PL 19053/0030

LAY SUMMARY

The MHRA granted Tenlec Pharma Limited a Marketing Authorisation for the medicinal product Human Albumin 200 g/l solution for infusion on 29th November 2012. This medicine is subject to restricted medical prescription and is indicated for the restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated, and use of a colloid is appropriate; the choice of albumin rather than artificial colloid will depend on the clinical situation of the individual patient, based on official recommendations.

Human Albumin 200 g/l solution for infusion contains, as its active, 200 g/l of total protein of which at least 95% is human albumin.

This application was submitted as an abridged complex national application under Article 10(a) according to Directive 2001/83/EC, as amended; a well-established use application.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of using Human Albumin 200 g/l solution for infusion outweigh the risks, hence a Marketing Authorisation has been granted.
Human Albumin 20 g/l Solution for Infusion

(Human Albumin)

PL 19053/0030

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction P4
Pharmaceutical assessment P5
Pre-clinical assessment P10
Clinical assessment P11
Overall conclusions and risk benefit assessment P13
INTRODUCTION

Based on the review of data on quality, safety and efficacy the UK granted a Marketing Authorisation to Tenlec Pharma Limited for the medicinal product Human Albumin 200 g/l solution for infusion on 29th November 2012. This product is a restricted prescription only medicine.

This application was submitted as a stand-alone abridged complex national application under Article 10(a) according to Directive 2001/83/EC, as amended; a well-established use application.

Human Albumin 200 g/l solution for infusion is indicated for the restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated, and use of a colloid is appropriate; the choice of albumin rather than artificial colloid will depend on the clinical situation of the individual patient, based on official recommendations.

Human Albumin 200 g/l solution for infusion contains, as its active, 200 g/l of total protein of which at least 95% is human albumin. Each vial of 50 ml contains 10 g of human albumin and each vial of 100 ml contains 20 g of human albumin.

No new clinical or preclinical data were submitted nor were they necessary for this application. The application was granted on 29th November 2012.
QUALITY ASSESSMENT

I  REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORISATION

The albumin product is manufactured from plasma collected and fractionated in Hungary. There are several collection centres, each of which has been inspected by the Hungarian authorities. Copies of the inspection reports have been provided but these are in Hungarian. English translations have been provided.

Details of the fractionation site have been provided and this facility has been inspected by the Hungarian National Institute of Pharmacy and the company has provided an English translation of the inspection report.

II  INTRODUCTION

This is a national application for a human albumin product isolated from plasma using classical cold ethanol fractionation. The proposed indication is for the restoration and maintenance of circulating blood volume.

III  DRUG SUBSTANCE

III.1  GENERAL INFORMATION

III.1.1  MANUFACTURE

Manufacture of the finished product is via a continuous process and for this reason there is no distinct Drug Substance.

III.1.2  CHARACTERISATION

Not applicable.

III.1.3  CONTROL OF DRUG SUBSTANCE


PLASMA MASTER FILE

The Plasma Master File adequately describes the processes in place and as such is satisfactory. All outstanding issues have been addressed by the Applicant and updated critical documents have been submitted as requested. A condition of grant is that the MAH submit their annual PMF updates. Any changes to the granted PMF (B-QA-MD-003, Edition 05) should be submitted to the Agency in the form of appropriate post-approval variations.
IV. Drug Product

IV.1 DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

Human Albumin 20% solution for infusion is an aqueous solution of protein obtained from human plasma that complies with the requirements of European Pharmacopoeia. It is a clear, slightly viscous, yellow or green liquid, filled in 50 mL and 100 mL, colourless, type II surface treated glass vials.

Composition of Human Albumin 20% solution for infusion 50 mL and 100 mL

<table>
<thead>
<tr>
<th>Component</th>
<th>50 mL presentation</th>
<th>100 mL presentation</th>
<th>Function</th>
<th>Reference standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human albumin</td>
<td>10.0 g</td>
<td>20.0 g</td>
<td>active substance</td>
<td>Ph. Eur. ¹)</td>
</tr>
<tr>
<td>Sodium caprylate</td>
<td>0.133 g</td>
<td>0.266 g</td>
<td>Stabiliser</td>
<td>Ph. Eur. ¹)</td>
</tr>
<tr>
<td>N-acetyl-DL-tryptophane</td>
<td>0.197 g</td>
<td>0.394 g</td>
<td>Stabiliser</td>
<td>Ph. Eur. ¹)</td>
</tr>
<tr>
<td>Sodium chloride (calc. as Sodium ion)</td>
<td>ad 7.25 mmol</td>
<td>ad 14.5 mmol</td>
<td>Isotoniser</td>
<td>Ph. Eur. ¹)</td>
</tr>
<tr>
<td>Water for injection</td>
<td>ad 50 ml</td>
<td>ad 100 ml</td>
<td>Solvent</td>
<td>Ph. Eur. ¹)</td>
</tr>
</tbody>
</table>

¹) Current edition

Container
Human Albumin 20% solution for infusion is filled into colourless, type II surface treated glass vials (50 ml and 100 ml), and closed with bromobutyl rubber stoppers and an aluminium cap. All components are in compliance with Ph.Eur.

IV.2. PHARMACEUTICAL DEVELOPMENT

The manufacturing process is carried out using classical ethanol fractionation. The applicant has not discussed any formulation development studies but the formulation is the same as other commercial albumin products.

IV.3. MANUFACTURE

Description of Manufacturing Process and Process Controls

The manufacturing of Human Albumin 20% solution for infusion is via a continuous process. A detailed description of the process has been provided, together with a flow chart. This is adequate.

Batch formula
The exact composition of the manufacturing batch cannot be given due to the nature of the starting material, therefore the given quantities are for guidance only. The exact quantities are determined by calculations based on the results of in-process control tests. The final concentration of the product is 20% solution and dilution is carried out based on the IPC protein results.
Ingredient quantities for a standard commercial batch size have been provided and are satisfactory.

**Control of critical steps and intermediates**

**Control of critical steps**

Based on manufacturing experience, specifications have been set for the critical parameters such as ethanol and protein concentration, pH, and ionic strength and these have been provided. These parameters are monitored in process at several timepoints.

**Control of intermediates**

Fraction V precipitate and the ultrafiltrate are considered to be intermediates and the stability of these has been investigated. Specifications of the ultrafiltrate and bulk solution have been provided and are satisfactory.

**Analytical procedures**

Tests are performed according to Ph. Eur. except determination of bioburden content. Bioburden count is checked during the manufacturing process of Human Albumin 20% solution for infusion. Full descriptions of the methods have been provided.

**Control of excipients**

The test procedures for all but one of the excipients follow the relevant Ph. Eur. Monograph. This is acceptable.

**IV.4 CONTROL OF DRUG PRODUCT**

**Specification**

The release specifications for Human Albumin 20% Solution for infusion have been provided.

The testing and specifications comply with the Ph.Eur.monograph for human albumin. The majority of the test methods are in accordance with Ph.Eur. In-house methods have been developed for the measurement of the two stabilisers sodium caprylate and N-acetyl-DL-tryptophan and validation reports have been provided. The finished product specifications are considered to be acceptable.

**Batch analyses**

The results from several consecutive batches have been supplied for each presentation. All the test results are within specifications and consistency between batches has been adequately demonstrated.

**Reference Standards or Materials**

Details of all biological reference preparations used for the analytical procedures have been provided.
CONTAINER CLOSURE SYSTEM

Human Albumin 20% solution for infusion is filled into 50 ml or 100 ml clear glass vials sealed with a bromobutyl rubber stopper and an aluminium cap. Full details, including supplier information have been provided.

STABILITY

Two stability studies have been carried out on Human Albumin 20%. Based on the available stability data a shelf- life of 36 months is proposed.

Labelling of storage conditions: “Store in a refrigerator at a temperature between +2 and +8 °C. Do not freeze. Keep the container in the outer carton in order to protect from light.”

The proposed shelf life is justified based on the stability data.

Stability studies have also been carried out on two process intermediates, Fraction V precipitate and the Albumin Ultrafiltrate. The proposed shelf life of the Fraction V precipitate and Albumin Ultrafiltrate intermediates is justified based on the stability data.

Post-approval Stability Protocol and Stability Commitment

The stability study under long term conditions of the batches listed in the dossier will be continued according to the post-approval stability protocol.

The post-approval commitments are noted.

V. APPENDICES

A.1 Facilities and Equipment

Facilities and equipment have been described in the manufacturing section of the dossier.

A.2 Adventitious Agents Safety Evaluation

The measures taken to minimise viral contamination of Human Albumin 20% include testing of the blood donors for viral markers as detailed in the Plasma Master File. The design of the viral validation studies and the selection of viruses are in accordance with the guidelines.

Based on the results obtained with porcine parvovirus (PPV), it is considered that the viral removal/inactivation of some non- lipid enveloped viruses may be limited. A statement to reflect this has been included in the SPC.

A.3 Novel Excipients

Not applicable.
REGIONAL INFORMATION

Medicinal products containing or using in the manufacturing process materials of animal and/or human origin

The manufacture of the finished product is a continuous process with Human Plasma as starting material and Human Albumin 20% solution for infusion as finished product. This application relates to a medicinal product, which contains or uses in the manufacture materials of human origin. Human plasma has therefore been listed as an active substance.

The applicant has provided a statement of compliance with regard to the NfG on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy via Human and Veterinary Products. No raw material of ruminant origin is used in the manufacture of Human Albumin 20%.

ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY

The manufacture of Human Albumin 20% is carried out using classical ethanol fractionation and consistency in the production process has been demonstrated. The finished product complies with the Ph.Eur. monograph on Human Albumin. All outstanding points have been addressed by the Applicant and updated critical documents have been submitted. A condition of grant is that the Company submit their annual PMF updates. Any changes to the granted PMF (B-QA-MD-003, Edition 05) should be submitted to the Agency in the form of appropriate post-approval variations.
PRECLINICAL ASSESSMENT

I. INTRODUCTION

This is a bibliographic application submitted for a national approval in the UK for human albumin.

I.1 GLP ASPECTS

As no new preclinical studies were conducted, GLP issues do not arise.

II. NON-CLINICAL DATA

No new experimental data on the product were submitted. The preclinical data set provided is a review of published material. These are essentially insufficient to establish the safety of the product. Safety assessment rests on clinical experience of the use of human albumin.

III. SUMMARY OF PRODUCT CHARACTERISTICS

Sections 4.6 and 5.3 of the SPC are acceptable without amendment.

IV. PHARMACO-TOXICOLOGICAL EXPERT REPORT

The author of the report is not identified. However, it is indicated that it was prepared by Medix Clinical and Consulting Services, of Budapest. It is acceptable.

V. CONCLUSION

There are no preclinical objections to the grant of a Product Licence.
CLINICAL ASSESSMENT REPORT

I INTRODUCTION

This is a stand-alone, bibliographical, initial, national product licence application for a human albumin product which is manufactured in Hungary, released in the UK by NIBSC, presumably to be distributed by the proposed Marketing Authorisation Holder, Tenlec Pharma Ltd. This application is to the UK only with no intention to proceed to MRP. The application was made in 2004, prior to certain revisions of Guidance documents.

The proposed indication ("Restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated, and use of a colloid is appropriate") is that included in the Core SPC for Human Albumin Solution as revised and adopted in November 2005 as a result of CHMP review of the results of the SAFE study, showing equivalent efficacy of human albumin and normal saline when used for intravascular volume resuscitation.

No clinical trial data is submitted. The application is supported by an exhaustive literature review which demonstrates the established clinical use of human albumin in terms of clinical pharmacology, efficacy and safety. Since this established use is agreed, this assessment concentrates on the technical leaflets supplied.

A proposed SPC, Prescriber leaflet (PL) and Patient information leaflet (PIL) have been provided. The PL is identical to the SPC. The SPC is largely in line with the Core SPC for Human Albumin Solution CPMP/PhVWP/BPWG/2231/00/Rev 2 and the NfG on the Warning on Transmissible Agents in SPCs and Package Leaflets for Plasma-derived Medicinal Products (CPMP/BPWG/BWP/561/03).

II SCIENTIFIC EVIDENCE

II.1 CLINICAL PHARMACOLOGY

Based on literature review (see above), the established clinical pharmacology of human albumin was satisfactorily summarised.

II.2 EFFICACY

Based on literature review (see above), the established efficacy of human albumin in various indications in addition to the proposed indication was satisfactorily and critically summarised.

II.3 SAFETY

Based on literature review (see above), the established safety of human albumin was satisfactorily and critically summarised.
PROPOSED SUMMARY OF PRODUCT CHARACTERISTICS AND PRESCRIBER LEAFLET

The proposed Prescriber Leaflet is the same as the proposed SPC and they are satisfactory.

III CONCLUSIONS

The applicant has made the necessary changes to the SPC and PIL. This is acceptable. There are no more clinical objections to approval of this application.

Decision:
Approved.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of human albumin 200 g/l solution for infusion are well defined and controlled. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRE-CLINICAL
No new preclinical data were submitted and none are required for an application of this type.

EFFICACY
Based on a review of the literature, the established efficacy and safety of human albumin was satisfactorily and critically summarised.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety data were submitted. Extensive clinical experience with human albumin 200 g/l solution for infusion is considered to have demonstrated the therapeutic value of the product. The risk: benefit is, therefore, considered to be positive.
MHRA PAR - Human Albumin 20 g/l Solution for Infusion

(Human Albumin)

PL 19053/0030

**STEPS TAKEN FOR ASSESSMENT**

1. The MHRA received the marketing authorisation application 22\textsuperscript{nd} December 2004.
2. Following standard checks the MHRA informed the applicant that its application was considered valid on 10\textsuperscript{th} February 2005.
3. Following assessment of the submitted data, the MHRA sent a request for further information (RFI) to the MAH on 21\textsuperscript{st} March 2005.
4. The MHRA received a response from the MAH on 12\textsuperscript{th} September 2006.
5. Following assessment of the submitted data, the MHRA sent a RFI to the MAH on 18\textsuperscript{th} September 2006.
6. The MHRA received a response from the MAH on 10\textsuperscript{th} November 2009.
7. Following assessment of the submitted data, the MHRA sent a RFI to the MAH on 13\textsuperscript{th} April 2011.
8. The MHRA received a response from the MAH on 18\textsuperscript{th} July 2011.
9. Following assessment of the responses the MHRA sent a further RFI to the MAH on 15\textsuperscript{th} September 2011.
10. The MHRA received a response from the MAH on 14th December 2011.
11. Following assessment of the responses the MHRA granted the application on 29\textsuperscript{th} November 2012.
Human Albumin 20 g/l Solution for Infusion

(Human Albumin)

PL 19053/0030

**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
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Human Albumin 20 g/l Solution for Infusion

(Human Albumin)

PL 19053/0030

SUMMARY OF PRODUCT CHARACTERISTICS
1 NAME OF THE MEDICINAL PRODUCT

Human Albumin 200 g/l solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human Albumin 200 g/l solution for infusion is a solution containing 200 g/l of total protein of which at least 95% is human albumin.

Each vial of 50 ml contains 10 g of human albumin.
Each vial of 100 ml contains 20 g of human albumin.

Excipient(s):
This medicinal product contains 138-152 mmol sodium per litre. To be taken into consideration by patients on a controlled sodium diet.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.
A clear, slightly viscous liquid; it is almost colourless, yellow, amber or green.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated, and use of a colloid is appropriate.
- The choice of albumin rather than artificial colloid will depend on the clinical situation of the individual patient, based on official recommendations.

4.2 Posology and method of administration

The concentration of the albumin preparation, dosage and the infusion-rate should be adjusted to the patient's individual requirements.

Posology
The dose required depends on the size of the patient, the severity of trauma or illness and on continuity of fluid and protein losses. Measures of adequacy of circulating volume and not plasma albumin levels should be used to determine the dose required.
If human albumin is to be administered, haemodynamic performance should be monitored regularly; this may include:
- arterial blood pressure and pulse rate
- central venous pressure
- pulmonary artery wedge pressure
- urine output
- electrolyte
- haematocrit/haemoglobin

**Method of administration**
Human albumin can be directly administered by the intravenous route, or it can also be diluted in an isotonic solution (e.g. 5 % glucose or 0.9 % sodium chloride).

The infusion rate should be adjusted according to the individual circumstances and the indication.

In plasma exchange the infusion-rate should be adjusted to the rate of removal.

**4.3 Contraindications**

Hypersensitivity to albumin preparations or to any of the excipients.

**4.4 Special warnings and precautions for use**

Suspicion of allergic or anaphylactic type reactions requires immediate discontinuation of the injection. In case of shock, standard medical treatment for shock should be implemented.

Albumin should be used with caution in conditions where hypervolaemia and its consequences or haemodilution could represent a special risk for the patient. Examples of such conditions are:
- Decompensated cardiac insufficiency
- Hypertension
- Oesophageal varices
- Pulmonary oedema
- Haemorrhagic diathesis
- Severe anaemia
- Renal and post-renal anuria

The colloid-osmotic effect of Human albumin 200 g/l solution for infusion is approximately four times that of blood plasma. Therefore, when concentrated
albumin is administered, care must be taken to assure adequate hydration of the patient. Patients should be monitored carefully to guard against circulatory overload and hyperhydration.

200-250 g/l Human albumin solution are relatively low in electrolytes compared to the 4 - 5% human albumin solutions. When albumin is given, the electrolyte status of the patient should be monitored (see section 4.2) and appropriate steps taken to restore or maintain the electrolyte balance.

Albumin solutions must not be diluted with water for injections as this may cause haemolysis in recipients.

If comparatively large volumes are to be replaced, controls of coagulation and haematocrit are necessary. Care must be taken to ensure adequate substitution of other blood constituents (coagulation factors, electrolytes, platelets and erythrocytes).

Hypervolaemia may occur if the dosage and rate of infusion are not adjusted to the patients circulatory situation. At the first clinical signs of cardiovascular overload (headache, dyspnoea, jugular vein congestion), or increased blood pressure, raised venous pressure and pulmonary oedema, the infusion is to be stopped immediately.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

There are no reports of virus transmissions with albumin manufactured to European Pharmacopoeia specifications by established processes.

It is strongly recommended that every time that Human Albumin 200 g/l solution for infusion is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.
4.5 Interaction with other medicinal products and other forms of interaction

No specific interactions of human albumin with other medicinal products are known.

4.6 Fertility, pregnancy and lactation

The safety of Human Albumin 200 g/l solution for infusion for use in human pregnancy has not been established in controlled clinical trials. However, clinical experience with albumin suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected.

No animal reproduction studies have been conducted with Human Albumin 200 g/l solution for infusion.

However, human albumin is a normal constituent of human blood.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

Mild reactions such as flush, urticaria, fever, and nausea occur rarely. These reactions normally disappear rapidly when the infusion rate is slowed down or the infusion is stopped. Very rarely, severe reactions such as shock may occur. In these cases, the infusion should be stopped and an appropriate treatment should be initiated.

For safety with respect to transmissible agents, see section 4.4.

4.9 Overdose

Hypervolaemia may occur if the dosage and rate of infusion are too high. At the first clinical signs of cardiovascular overload (headache, dyspnoea, jugular vein congestion), or increased blood pressure, raised central venous pressure and pulmonary oedema, the infusion should be stopped immediately and the patient's haemodynamic parameters carefully monitored.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: plasma substitutes and plasma protein fractions,
ATC code: B05AA01.
Human albumin accounts quantitatively for more than half of the total protein in the plasma and represents about 10% of the protein synthesis activity of the liver.

Physico-chemical data: Human albumin 200 g/l has a corresponding hyperoncotic effect.

The most important physiological functions of albumin results from its contribution to oncotic pressure of the blood and transport function. Albumin stabilises circulating blood volume and is a carrier of hormones, enzymes, medicinal products and toxins.

5.2 Pharmacokinetic properties

Under normal conditions, the total exchangeable albumin pool is 4-5 g/kg body weight, of which 40-45% is present intravascularly and 55-60% in the extravascular space. Increased capillary permeability will alter albumin kinetics and abnormal distribution may occur in conditions such as severe burns or septic shock.

Under normal conditions, the average half-life of albumin is about 19 days. The balance between synthesis and breakdown is normally achieved by feed-back regulation. Elimination is predominantly intracellular and due to lysosome proteases.

In healthy subjects, less than 10% of infused albumin leaves the intravascular compartment during the first 2 hours following infusion. There is considerable individual variation in the effect on plasma volume. In some patients the plasma volume can remain increased for some hours. However, in critically ill patients, albumin can leak out of the vascular space in substantial amounts at an unpredictable rate.

5.3 PRECLINICAL SAFETY DATA

Human albumin is a normal constituent of human plasma and acts like physiological albumin.

In animals, single dose toxicity testing is of little relevance and does not permit the evaluation of toxic or lethal doses or of a dose-effect relationship. Repeated dose toxicity testing is impracticable due to the development of antibodies to heterologous protein in animal models.

To date, human albumin has not been reported to be associated with embryo-foetal toxicity, oncogenic or mutagenic potential.

No signs of acute toxicity have been described in animal models.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium caprylate  16 mmol/l (2.7 g/l)
N-acetyl-DL-tryptophan  16 mmol/l (4.3 g/l)
sodium chloride (calc. Na+)  ad 145 mmol/l (3.35 g/l)
water for injection  ad 1 litre

6.2 Incompatibilities

Human albumin must not be mixed with other medicinal products (except those mentioned in section 6.6), whole blood and packed red cells.

6.3 Shelf life

3 years
After first opening the product must be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2°C–8°C).
Do not freeze.
Keep the container in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Each carton box contains one 50 ml or 100 ml glass vial, closed with bromobutyl rubber stopper and aluminium cap.

6.6 Special precautions for disposal

The solution should be directly administered by the intravenous route, or it can also be diluted in an isotonic solution (e.g. 5 % glucose or 0.9 % sodium chloride).

Albumin solutions must not be diluted with water for injections as this may cause haemolysis in recipients.
If large volumes are administered, the product should be warmed to room or body temperature before use.

The solution should be clear or slightly opalescent. Do not use solutions which are cloudy or have deposits. This may indicate that the protein is unstable or that the solution has become contaminated.

Once the container has been opened, the contents should be used immediately. Any unused product should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Tenlec Pharma Ltd.
Broadlands, Amberstone,
Hailsham, East Sussex
BN27 1PQ, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 19053/0030

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/11/2012

10 DATE OF REVISION OF THE TEXT

29/11/2012
PACKAGE LEAFLET: INFORMATION FOR THE USER

Human Albumin 20 g/l Solution for Infusion
Human Albumin

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others.
- It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:
1. What Human Albumin 20 g/l solution for infusion is and what it is used for
2. What you need to know before you use Human Albumin 20 g/l solution for infusion
3. How to use Human Albumin 20 g/l solution for infusion
4. Possible side effects
5. How to store Human Albumin 20 g/l solution for infusion
6. Contents of the pack and other information

1. What Human Albumin 20 g/l solution for infusion is and what it is used for

Your medicine has been made from blood plasma originating from screened donors. The product contains proteins, which are substances that occur naturally in your body and are needed for several different functions. The stabilised liquid in the glass vials contains approximately 200 grams per litre (200 g/l) of protein, of which at least 95% is human albumin (the active substance), stabilised with sodium caprylate and N-acetyl DL-lysophosphatidylcholine.

Each vial contains 50 ml or 100 ml of a 20 g/l solution of human albumin.

The medicine is used for the restoration and maintenance of circulating blood volume (if you lose a lot of fluid, you will need to have this replaced, which is what this medicine is intended for).

The product is an intravenous infusion (an injection given slowly into a vein) and is only available on a doctor’s prescription.

2. What you need to know before you use Human Albumin 20 g/l solution for infusion

Do not use Human Albumin 20 g/l solution for infusion
- if you are allergic (hypersensitive) to albumin preparation or any of the other ingredients of this medicine (listed in section 6).

Take special care with Human Albumin 20 g/l solution for infusion
- Tell your doctor if you:
  - have a allergic (hypersensitive) reaction to Human Albumin 20 g/l solution for infusion when injected. Treatment should be stopped immediately.
  - have high blood pressure (hypertension)
  - have heart problems when the heart is not pumping properly (heart failure)
  - have enlarged veins in the esophagus (oesophageal varices)
  - have fluid accumulation in the lungs
  - have blood problems, especially anemia, or a tendency to spontaneous bleeding
  - have severe kidney problems or a chronic liver condition

- are breast feeding your baby
- know that you are, or you think you might be pregnant
- are taking other medicine (although other medicines are unlikely to affect your treatment)

Other medicines and Human Albumin 20 g/l solution for infusion
- Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
- Pregnancy and breast-feeding
- Ask your doctor or pharmacist for advice before taking any medicine.

Important information about some of the ingredients of Human Albumin 20 g/l solution for infusion
- When medicines are made from human blood plasma, certain measures are put in place to prevent infections being passed on to patients. These include rigorous selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pool of plasma for signs of viral infections. Manufacturers of these products are also subject to stringent measures of control, and the product is supplied in order to maintain a record of the batches used.

There are no reports of virus infections with albumin manufactured to European Pharmacopoeia specifications by established processes.

- It is strongly recommended that every time you receive a dose of Human Albumin 20 g/l solution for infusion the name and batch number of the product are recorded in order to maintain a record of the batches used.

3. How to use Human Albumin 20 g/l solution for infusion

Your medicine will be given to you in hospital as an infusion (an injection given slowly into a vein). The product will be warmed to room temperature before it is given.

The amount needed will depend on the reason the medicine is being given and on how well you respond to the treatment. The dose will be calculated by your doctor. Tors will probably be carried out on your blood to check whether the right amounts of protein are present and treatment can stop.

Children: The amount given will depend on the age of your child. Your doctor will take this into account when working out the amount of medicine to give.

During and after treatment with Human Albumin 20 g/l solution for infusion, your doctor will check how well the medicine is working by taking your pulse and blood pressure and by testing your blood. Your heart and breathing will be checked regularly as these are good indications of whether you have too much fluid, particularly if you are elderly or very young. This checking may be continued even after the treatment has finished.

When large quantities of fluid are needed, the amounts of important substances normally lost in blood may go down too far. In this case, other types of fluid, such as plasma or red blood cells, may also be needed.
4.9 Overdose
Hyperlactaemia may occur if the dosage and rate of infusion are too high. All the first clinical signs of cardiovascular overload (headache, dyspnoea, jugular venous congestion), or increased blood pressure, raised central venous pressure and pulmonary oedema, the infusion should be stopped immediately and the patient's haemodynamic parameters carefully monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: plasma substitutes and plasma protein fractions. ATC code: B05A001.

Human albumin accounts quantitatively for more than half of the total protein in the plasma and represents about 10% of the protein synthesis activity of the liver.

Physicochemical data: Human albumin 200 g/l has a corresponding hyperoncotic effect.

The most important physiological functions of albumin result from its contribution to oncotic pressure of the blood and transport function. Albumin stabilises circulating blood volume and is a carrier of hormones, enzymes, medicinal products and toxins.

5.2 Pharmacokinetic properties
Under normal conditions, the total exchangeable albumin pool is 4.5 g/kg body weight, of which 40-45% is present intravascularly and 55-60% in the extravascular space. Increased capillary permeability will alter albumin kinetics and abnormal distribution may occur in conditions such as severe burns or septic shock.

Under normal conditions, the average half-life of albumin is about 19 days. The balance between synthesis and breakdown is normally achieved by feed-back regulation. Elimination is predominantly intracellular and due to lysosomal phagocytes.

In healthy subjects, less than 10% of infused albumin leaves the intravascular compartment during the first 2 hours following infusion. There is considerable individual variation in the effect on plasma volume. In some patients the plasma volume can remain increased for some hours. However, in critically ill patients, albumin can leak out of the vascular space in substantial amounts at an unpredictable rate.

5.3 Preclinical safety data
Human albumin is a normal constituent of human plasma and acts like physiological albumin.

In animals, single dose toxicity testing is of little relevance and does not permit the evaluation of toxic or lethal doses or of a dose-effect relationship. Repeated dose toxicity testing is impracticable due to the development of antibodies to heterologous protein in animal models.

To date, human albumin has not been reported to be associated with embryo-fetal toxicity, oncogenic or mutagenic potential.

No signs of acute toxicity have been described in animal models.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium caprylate 16 mmol/l (2.7 g/l) N-acetyl-DL-hydroxypropanol 16 mmol/l (4.3 g/l) Sodium chloride (calc. Na+) ad 146 mmol/l (3.35 g/l) Water for injection ad 1 litre

6.2 Incompatibilities
Human albumin must not be mixed with other medicinal products (except those mentioned in section 5.9), whole blood and packed red cells.

6.3 Shelf life
3 years
After first opening the product must be used immediately.

6.4 Special precautions for storage
Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the container in the outer carton in order to protect from light.
For storage conditions of the diluted medicinal product, see section 5.3.

6.5 Nature and contents of container
Each carton box contains one 50 ml or 100 ml glass vial, closed with bromobutyl rubber stopper and aluminium cap.

6.6 Special precautions for disposal and other handling
The solution should be directly administered by the intravenous route, or it can also be diluted in an isotonic solution (e.g. 5% glucose or 0.9% sodium chloride).

Albumin solutions must not be diluted with water for injections as this may cause haemolysis in recipients.
If large volumes are administered, the product should be warmed in a room or body temperature before use.

The solution should be clear or slightly opalescent. Do not use solutions which are cloudy or have deposits. This may indicate that the protein is unstable or that the solution has become contaminated.

Once the container has been opened, the contents should be used immediately. Any unused product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
Teretec Pharma Ltd.
Broadlands, Amberstone,
Hailsham, East Sussex
BN27 1PQ, UK

8. MARKETING AUTHORISATION NUMBER(S)
PL 19053/030

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
[To be completed nationally]

10. DATE OF REVISION OF THE TEXT
[To be completed nationally]
Method of administration
Human albumin can be directly administered by the intravenous route, or it can also be diluted in an isotonic solution (e.g. 5% glucose or 0.9% sodium chloride).
The infusion rate should be adjusted according to the individual circumstances and the indication. In plasma exchange the infusion rate should be adjusted to the rate of removal.

4.3 Contraindications
Hypersensitivity to albumin preparations or to any of the excipients.

4.4 Special warnings and precautions for use
Suspicion of allergic or anaphylactic type reactions requires immediate discontinuation of the injection. In case of shock, standard medical treatment for shock should be implemented.

Albumin should be used with caution in conditions where hypervolaemia and its consequences or haemodilution could represent a special risk to the patient. Examples of such conditions are:
- Decompensated cardiac insufficiency
- Hypertension
- Cerebrovascular accidents
- Pulmonary oedema
- Haemorrhagic diathesis
- Severe anaemia
- Renal and post-renal anuria

The colloid-osmotic effect of Human albumin 200 g/l solution for infusion is approximately four times that of blood plasma. Therefore, when concentrated albumin is administered, care must be taken to assure adequate hydration of the patient. Patients should be monitored carefully to guard against circulatory overload and hypervolaemia.

200-250 g/l Human albumin solution are relatively low in electrolytes compared to the 4-5% human albumin solutions. When albumin is given, the electrolyte status of the patient should be monitored (see section 4.2) and appropriate steps taken to restore or maintain the electrolyte balance.

Albumin solutions must not be diluted with water for injections as this may cause haemolysis in recipients.

If comparatively large volumes are to be replaced, controls of coagulation and haemostasis are necessary. Care must be taken to ensure adequate substitution of other blood constituents (coagulation factors, electrolytes, platelets and erythrocytes).

Hypervolaemia may occur if the dosage and rate of infusion are not adjusted to the patients circulatory situation. At the first clinical signs of cardiovascular overload (headache, dyspnoea, jugular vein congestion), or increased blood pressure, raised venous pressure and pulmonary oedema, the infusion is to be stopped immediately.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

There are no reports of virus transmissions with albumin manufactured to European Pharmacopeia specifications by established processes.

It is strongly recommended that every time that Human albumin 200 g/l solution for infusion is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

4.5 Interaction with other medicinal products and other forms of treatment
No specific interactions of human albumin with other medicinal products are known.

4.6 Pregnancy and lactation
The safety of Human albumin 200 g/l solution for infusion for use in human pregnancy has not been established in controlled clinical trials. However, clinical experience with albumin suggests that no harmful effects on the course of pregnancy, or on the fetus and the neonate are to be expected.

No animal reproduction studies have been conducted with Human albumin 200 g/l solution for infusion. However, human albumin is a normal constituent of human blood.

4.7 Effects on ability to drive and use machines
No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects
Wid reactions such as flush, urticaria, fever, and pruritus occur rarely. These reactions normally disappear rapidly when the infusion rate is slowed down or the infusion is stopped. Very rarely, severe reactions such as shock may occur. In these cases, the infusion should be stopped and an appropriate treatment should be initiated.

For safety with respect to transmissible agents, see section 4.4.
If you take more Human Albumin 20 g/l solution for infusion than you should
Your condition will be checked regularly while you are being given this medicine.
Signs of too much fluid being given are high blood pressure, difficulty in breath-
ing (particularly when lying down) and high pressure inside your heart, which
your doctor will measure. It is the unlikely event that too much medicine is given,
the infusions will be stopped immediately and your doctor may give you treatment
to remove the excess fluid.

4. Possible side effects

Like all medicines, Human Albumin 20 g/l solution for infusion can cause side
effects, although not everybody gets them.

Mild reactions may occur rarely. Some patients may feel sick, have a tempera-
ture or have flashes and itchy skin. These reactions normally disappear rapidly
when the infusion rate is slowed down or the treatment is stopped.

Very rarely, severe reactions such as shock (when your blood pressure falls
dangerously low) may occur. In these cases, the infusion will be stopped and a
treatment will be initiated by your doctor.

If you feel unwell or suffer from any of the side-effects mentioned above after
being given your medicine, you must tell your doctor.

5. How to store Human Albumin 20 g/l solution for infusion

Store in a refrigerator (2°C - 6°C).
Do not freeze.
Keep the container in the outer carton in order to protect from light.
Keep this medicine out of the sight and reach of children.
Each vial is intended to be used once only. Once the medicine's stopper is
perforated it should be used immediately.

Do not use Human Albumin 20 g/l solution for infusion after the expiry date
which is stated on the label after EXP. The expiry date refers to the last day
of that month.

Do not use solutions which are cloudy or have deposits. This may indicate that
the protein is unstable or that the solution has become contaminated.

Medicines should not be disposed of via wastewater or household waste. These
measures will help to protect the environment.

6. Contents of the pack and other information

What Human Albumin 20 g/l solution for infusion contains
- The active substance is Human albumin
- Human Albumin 20 g/l solution for infusion is a solution containing 20 g/l of
total protein of which at least 90% is human albumin.
- The other ingredients are sodium caprylate, N-acetyl-DL-tartaric amidino
sodium chloride and water for injection.

What Human Albumin 20 g/l solution for infusion looks like and
contents of the pack
The product is a clear, slightly viscous liquid, it is almost colorless, yellow,
amber or green.
Each carton box contains one 50 ml or 100 ml glass vials, closed with bromobu-
ty rubber stopper and aluminium cap.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation holder:
Tentec Pharma Ltd.
Broadlands, Amberstone, Hartfield, East Sussex
BN27 1PQ, UK

Manufacturer:
HUMANBiologics Manufacturing and Trading Limited Liability Company
Táncsics M. ut 80, H-2160 Gdána, Hungary

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Human Albumin 20 g/l Solution for Infusion

(Human Albumin)

PL 19053/0030

Labelling