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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE CORE SPC FOR HUMAN ALBUMIN SOLUTION (CPMP/PhVWP/BPWG/2231/99 rev.2)

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Note:

This guideline replaces the Core SPC on Human Albumin Solution, Reference (CPMP/PhVWP/BPWG/2231/99/Rev 1)

Revision 1 amended sections 1 and 2 of the Core SPC for Human Albumin Solution to express the strength in g/l instead of %. The opportunity was also taken to update quality aspects in line with the current Ph. Eur. monograph, the statement on treatment of shock in section 4.4, and the warning on transmissible agents.

Revision 2 adds a statement to the text preceding the Core SPC. There is no change to the Core SPC text itself.

REVISION OF THE CORE SPC FOR HUMAN ALBUMIN SOLUTION

The following explanatory statement was made by the CPMP in October 2000, when an amended version of the core SPC was adopted:

1. INTRODUCTION

In July 1998 the Cochrane Injuries Group published in the British Medical Journal (BMJ 1998; 317:235) a meta-analysis of clinical trials in critically ill patients treated with albumin, which showed a 6% increase in mortality compared with patients who had received crystalloids or no treatment. As a result of this publication, a review of the safety of human albumin products was undertaken by Member States and discussed at CPMP's Pharmacovigilance Working Party and Blood Products Working Group.

2. CPMP CONCLUSIONS

- There is insufficient evidence of hazard to warrant withdrawal of albumin products.
- The question of albumin and mortality will only finally be answered by conducting large, purpose-designed randomised controlled clinical trials.
- The CPMP Core Summary of Product Characteristics for human albumin should be updated in the light of this review to give a more specific indication and to highlight the risk of fluid overload by including appropriate warnings and precautions. In particular:
    i. The indication for human albumin should focus on the use of albumin to replace lost fluids i.e. "Restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated and use of a colloid is appropriate".
    ii. Dose recommendations should be removed from the SPC because these vary depending on the clinical situation.
    iii. The SPC should emphasise that haemodynamic parameters should be monitored in patients receiving albumin and should warn about the risk of hypervolaemia and cardiovascular overload.

3. REVISED CORE SPC

The core SPC for human albumin has been revised in line with the above recommendations. In addition, the remainder of the SPC has been updated in line with current practice.

In November 2005, in the light of new evidence, the CHMP decided to add the following statement:

In 2004 the results of the SAFE study were published[1]. This is a prospective, multi-centre, randomised, double-blind clinical trial to compare the effect of intravascular volume resuscitation with albumin or normal saline on mortality in a heterogeneous population of patients in ICU. 6997 patients who had been admitted to ICU were randomly assigned to receive either 4% albumin or normal saline for intravascular-fluid resuscitation during the next 28 days. The primary endpoint was death from any cause during the first 28 days. Equivalent rates of death were found in the two treatment groups: 20.9% (726 deaths) in the albumin group vs. 21.1% (729 deaths) in the saline group (relative risk of death 0.99, 95% C.I. 0.91-1.09, p=0.87).

The results of the SAFE study show no evidence that 4% human albumin solution causes excess mortality compared with normal saline when used for intravascular volume resuscitation. The authors conclude that albumin and saline should be considered therapeutically equivalent treatments in the

[1] The SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the Intensive Care Unit. N Engl J Med 2004;350:2247-2256.

patient group studied. This is in line with the approved indication in the core SPC to restore and maintain blood volume where volume deficiency has been demonstrated and where individualised treatment and careful monitoring are carried out.

This corroborates the decisions made by the CPMP in 2000, not to withdraw albumin products from the market and to amend parts 4.1, 4.2 and 4.4 concerning indication, individualised treatment and monitoring.

A new meta-analysis including the SAFE study by the Cochrane Collaboration[2] finds no evidence that albumin increases mortality in patients with hypovolaemia.

Predefined sub-group analyses were performed for patients with trauma, severe sepsis, and acute respiratory distress syndrome as part of the SAFE study. There was a trend towards increased mortality in patients with trauma treated with albumin, which was due to a worse outcome in those patients with trauma and associated brain injury. Conversely, there was a trend towards a better outcome with albumin in patients with severe sepsis. Both these trends should be interpreted with caution. Specifically designed and appropriately powered studies are needed to establish whether these are real treatment effects or due to chance.

It should be noted that patients less than 18 years and patients admitted to the ICU after cardiac surgery, after liver transplantation, or for the treatment of burns were excluded and, therefore, no conclusions on comparative safety of 4% albumin and normal saline in these groups can be drawn from the SAFE study.

[2] The albumin reviewers. Human albumin solution for resuscitation and volume expansion in critically ill patients (Review). The Cochrane database of Systematic Reviews 2004, Issue 4. Art. No. CD001208.pub2.

CORE SPC
FOR
HUMAN ALBUMIN SOLUTION

The QRD Product Information template with explanatory notes and the convention to be followed for QRD templates** provide general guidance on format and text and should be read in conjunction with the core SPC and the Guideline on Summary of Product Characteristics.*
*In addition, for the content of sections 4.4 and 4.8 concerning transmissible agents, refer to the current version of the "Note for Guidance on the Warning on Transmissible Agents in SPCs and Package Leaflets for plasma-derived medicinal products" (CPMP/BPWG/BWP/561/03).****

The following convention is used in this core SPC:
- <wave-underlined text> for 40 – 50 g/l albumin
- <dot-underlined text> for 200 - 250 g/l albumin

* http://www.emea.eu.int/htms/human/qrd/qrdplt/H01a%20EN%20NOTE%20SPC-II-lab-pl%20v6.pdf
** http://www.emea.eu.int/htms/human/qrd/qrdplt/qrdconventionv6.pdf
*** http://www.emea.eu.int/pdfs/human/bpwg/056103en.pdf

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name of product <strength in g/l> <pharmaceutical form>}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

{(Invented) name of product <strength in g/l>} is a solution containing {X}g/l <{X/10} %> of total protein of which at least 95% is human albumin.

[for a transition period, the strength can also be expressed in units other than g/l]

<A vial of x ml contains {Y}g of human albumin.>

[Product specific: specify if mildly hypooncotic or hyperoncotic]

For 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 continuing 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 special 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 or 250 g/l 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.>

200-250g/l Human albumin solutions are relatively low in electrolytes compared to the 40-50 g/l 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.

[The text to be inserted here for transmissible agents should be in accordance with the current version of the guideline on the Warning on Transmissible Agents in SPCs and Package Leaflets for plasma-derived medicinal products (CPMP/BPWG/BWP/561/03).]

4.5 Interactions with other medicinal products and other forms of interactions

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

4.6 Pregnancy and lactation

The safety of {(trade) name of the product} 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 {(trade) name of product}.>

<Experimental animal studies are insufficient to assess the safety with respect to reproduction, development of the embryo or foetus, the course of gestation and peri-and postnatal development.> However, human albumin is a normal constituent of human blood.

4.7 Effect 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.

[The text to be inserted here for transmissible agents should be in accordance with the current version of the guideline on the Warning on Transmissible Agents in SPCs and Package Leaflets for plasma-derived medicinal products (CPMP/BPWG/BWP/561/03).]

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 {40 to 50g/l} is mildly hypooncotic to normal plasma.> <Human albumin 200 or 250 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 feedback 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

[Product specific, in addition, the name and concentration of any added substances (e.g. stabiliser); the content of sodium expressed in millimoles per litre]

6.2 Incompatibilities

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

[Product specific]

6.3 Shelf-life

[Product specific]

6.4 Special precautions for storage

[Product specific]

<Store in the original container> <Keep the container in the outer carton> in order to protect from light.

6.5 Nature and contents of container

[Product specific]

6.6 Instructions for use and handling and disposal

The solution 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)>.

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.

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

{Name and address}

8. MARKETING AUTHORISATION NUMBER(S)

[Product specific]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[Product specific]

10. DATE OF REVISION OF TEXT

[Product specific]