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Guideline on core SmPC for human albumin solution (EMA/CHMP/BPWP/494462/2011/Rev.3)

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This guideline (EMA/CHMP/BPWP/494462/2011/Rev.3) replaces guideline on core SPC with reference number CPMP/PhVWP/BPWG/2231/99/Rev.2

Keywords	***Human albumin, restoration and maintenance of circulating blood volume, volume deficiency, colloid***

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Guideline on core SmPC for human albumin solution

Table of contents

Executive summary

This guideline describes the information to be included in the Summary of Product Characteristics (SmPC) for human albumin solution.

1. Introduction (background)

The purpose of this core SmPC is to provide applicants and regulators with harmonised guidance on the information to be included in the Summary of Product Characteristics (SmPC) for human albumin solution.

This core SmPC addresses specific aspects related to human albumin solution, for general wording and structural aspects, the SmPC guideline and QRD template should be followed. The QRD product information template with explanatory notes ('QRD annotated template')[1] and the convention to be followed for QRD templates[2] provide general guidance on format and text and should be read in conjunction with the core SmPC and the Guideline on summary of product characteristics[3].

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 SmPCs and Package Leaflets for plasma-derived medicinal products" (EMA/CHMP/BWP/360642/2010 rev. 1).[4]

The following convention is used in this core SmPC:

- <wave-underlined text> for 40 – 50 g/l albumin

- <dot-underlined text> for 200 - 250 g/l albumin

Timeline history of core SmPC: The original core SPC (CPMP/PhVWP/BPWG/2231/99) came into effect in April 2001.

Revision 3 deletes the text preceding the Core SmPC, Section 4.1. Therapeutic indications is amended by deleting the wording "The choice of albumin rather than artificial colloid will depend on the clinical situation of the individual patient, based on official recommendations"

2. Scope

This core SmPC covers human albumin solution defined by the Ph. Eur. Monograph (0255)

3. Legal basis

This guideline has to be read in conjunction with Article 11 of Directive 2001/83 as amended, and the introduction and general principles (4) and part I of the Annex I to Directive 2001/83 as amended.

[1] http://www.ema.europa.eu/htms/human/qrd/docs/Hannotatedtemplate.pdf
[2] http://www.ema.europa.eu/htms/human/qrd/docs/convention.pdf
[3] http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf
[4] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/12/WC500119001.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.

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

[Product specific: specify if mildly hypooncotic or hyperoncotic]

<Excipient(s) with known effect:>

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.
[It should be stated in which age groups the product is indicated, specifying the age limits, e.g. 'X is indicated in <adults><neonates><infants><children> <adolescents> <aged x to y <years, months>>.]

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 precautions for use

[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 SmPCs and Package Leaflets for plasma-derived medicinal products (EMA/CHMP/BWP/360642/2010).]

Suspicion of allergic or anaphylactic type reactions requires immediate discontinuation of the infusion. 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.

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 Fertility, pregnancy and lactation

Pregnancy
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 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.

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 Special precautions for disposal <and other handling>

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]