1. NAME OF THE MEDICINAL PRODUCT

HAES-steril® 6 %

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1000 ml contain:

Active ingredients:

Poly(O-2-hydroxyethyl)starch (Molar substitution 0.43 - 0.55) (Mean molecular weight: 200,000)	60.00 g
Sodium Chloride	9.00 g
Na^+ 154 mmol/l Cl^- 154 mmol/l	
Theoretical osmolarity	308 mosml/l
pH	3.5 - 6.0
Titratable Acidity	< 1.0 mmol NaOH/I

3. PHARMACEUTICAL FORM

Solution for intravenous infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Therapy and prophylaxis of volume deficiency (hypovolaemia) and shock (volume replacement therapy) in connection with:

  - Surgery (haemorrhagic shock)
  - Injuries (traumatic shock)
  - Infections (septic shock)
  - Burns (burn shock)

- Reduction in need for donor blood during surgery e.g. acute normovolaemic haemodilution = ANH

- Therapeutic dilution of blood (haemodilution).

4.2 Posology and method of administration

For intravenous infusion.

The initial 10 - 20 ml of HAES-steril 6% are to be infused slowly, keeping the patient under close observation (due to possible anaphylactoid reactions).
The daily dose and rate of infusion are to be determined according to blood loss and haemoconcentration. The effect of dilution limits the therapeutic application.

The use of colloidal plasma expanders in patients without cardiovascular or pulmonary risks is limited by a haematocrit of 30%.

Overloading of the circulatory system from too rapid and too high dosage must be avoided.

Recommended dosage for the therapy and prophylaxis of volume deficiency (hypovolaemia) and shock (volume substitution therapy):

Unless otherwise prescribed according to volume needs:

Maximum daily dose:
33 ml/kg BW/day
(= 2 g HES/kg BW/day, or
= 2500 ml/75 kg BW/day)

Maximum rates of infusion:
20 ml/kg BW/hour
(= 1500 ml/75 kg BW/hour)
(= 1.2 g HES/kg BW/hour)

Recommended dosage for reduction of donor blood during surgery (acute normovolaemic haemodilution - ANH):

Unless otherwise prescribed, substitution of autologous blood immediately prior to surgery at target haematocrit values after ANH not below 30%. Substitution at a ratio of 1:1 (HAES-steril 6% blood):

Daily dose:	2 - 3 x 500 ml (HAES-steril 6%)
Blood-letting:	2 - 3 x 500 ml (autologous blood)
Infusion rates:	1000 ml/15 - 30 min
Blood withdrawal rates:	1000 ml/15 - 30 min

Recommended dosage for haemodilution therapy:

Aim of the haemodilution therapy is the haematocrit decrease. Administration could be done isovolaemic (with blood-letting) or hypervolaemic (without blood-letting) with low (250 ml), medium (500 ml) or high dosage (2 x 500 ml).

Daily dose:	Infusion rates:
250 ml/day (low)	250 ml in 0.5 - 2 hours
500 ml/day (medium)	500 ml in 4 - 6 hours
2 x 500 ml/day (high)	2 x 500 ml in 8 - 24 hours

Duration of treatment:

Therapy and prophylaxis of volume deficiency (hypovolaemia) and shock (volume substitution therapy):

There is no pharmacological or clinical evidence to give cause for concern with regard to a repeated application. The duration and extent of the treatment are to be determined according to the duration and extent of the hypovolaemia.

Reduction of donor blood during surgery (acute normovolaemic haemodilution = ANH):

ANH is usually performed once prior to surgery.

Repeated use is possible if the initial haematocrit is within the normal range.

Haemodilution therapy:

The haemodilution therapy with HAES-steril 6% is recommended for up to 10 days.

4.3 Contraindications

- Severe congestive heart failure (cardiac insufficiency)
- Renal failure (serum creatinine > 2 mg/dl or > 177 mol/l)
- Severe coagulation disturbances (except in life-threatening emergencies)
- Excess fluid overload (hyperhydration) and severe lack of fluid (dehydration)
- Bleeding of the brain (cerebral haemorrhage)
- Starch allergy

4.4 Special warnings and special precautions for use

Serum creatinine levels should be monitored at the beginning of therapy.

Daily monitoring of the fluid balance and renal retention values is essential with limit-value creatinine values (1.2 - 2.0 mg/dl and 106 - 177 µmol/l, compensatory renal insufficiency).

Despite normal serum creatinine values, pathological urine findings can indicate existing compensatory renal damage. In such cases serum creatinine values should be monitored daily.

Where serum creatinine values and urine test results are normal, monitoring of renal retention values 1 - 2 times is essential in a therapy of several days duration.

Sufficient supply of fluid (2 - 3 litres of fluid per day) must be ensured.

Particular care must be taken with pulmonary oedema or chronic liver diseases.

In the literature a correlation between dose and frequency of itching in patients with otoneurological disorders, such as sudden deafness, tinnitus ("ringing in the ear"), or acoustic trauma, has been described. In such cases it is advisable to reduce the dose to a maximum of 500 ml/day. This will reduce the risk of itching as a side effect. It should also be ensured that the patient has an adequate fluid intake.

There are no data available as yet with regard to the use in children.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions with other drugs are known to date.

4.6 Pregnancy and lactation

There are no data available as yet with regard to use during pregnancy and breast-feeding. To be administered only where indication is vital during early pregnancy.

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

The product may lead to anaphylactoid reactions in isolated cases. In the event of intolerance reactions (see table) infusion is to be discontinued immediately and the standard emergency measures initiated:

Table

Clinical symptoms and degree of severity		Emergency measures	
I. Skin reactions	Stop of infusion	Antihistamines	
II. Tachycardia Drop in blood pressure Vertigo Nausea Vomiting	ALARM	Positioning	Antihistamines + corticosteroids e.g. 120 mg prednisolone i.v.
III. Shock Bronchospasm		Positioning Resuscitation	1. Adrenaline 0.05 - 0.1 mg i.v. + 2. Corticosteroids, e.g. prednisolone 1.0-2.0 9 i.v. 3. Infusion, e.g. albumin 5%
IV. Respiratory and cardiac arrest			

Modified from F.W. AHNEFELD

Long-term daily administration of HAES-steril 6% in medium and high doses frequently causes an almost untreatable itching. This can still occur weeks after ending the therapy, persist over months and could be arduous for the patient. Only in a rare number of cases were pains in the kidney area reported. In such cases, infusion is to be discontinued immediately, sufficient fluid supplied and the serum creatinine values monitored closely.

In higher doses, a prolongation of bleeding time can occur due to the dilution effect but clinically-relevant haemorrhage is not triggered. The fall in haematocrit and the dilution of the plasma proteins should be monitored.

The concentration of serum amylase can rise under administration of hydroxyethyl starch (interference with the diagnosis pancreatitis). A regular control of serum ionogramm and fluid balance is necessary.

4.9 Overdose

In cases of accidental overload the infusion has to be stopped and diuretics might be administered.

In serious and very serious cases of anaphylactoid reactions adrenaline has shown best efficacy and is drug of choice therefore. In case of breathing difficulties and imminent or manifest shock the following proceeding is recommended:

Venous or central venous access; fractional i.v. administration of 0.1% adrenaline diluted in NaCI solution (0.1 - 0.3 ml); give high doses of corticosteroids (e.g. 30 - 40 mg/kg BW prednisolone); volume substitution under replacement of the plasma substitute; application of oxygen by a nasal probe; if necessary, artificial respiration by mask or intubation; reanimation measures (in case of respiratory standstill or cardiac arrest).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC-Code: B05A A

Pharmacotherapeutic group: Plasma substitues and plasma protein fractions.

Hydroxyethyl starch (HES) solutions are artificial colloidal plasma expanders. Their effect on intravascular volume expansion and haemodilution depends on the degree of substitution and substitution pattern, the molecular weight and the concentration as well as dosage and infusion rate of the HES medicament.

Rapid infusion (approx. 500 ml within 20 min) of HAES-steril® 6% results in a plateau-like non-expansive increase of plasma volume by approx. 100 percent of the infused volume over 3 - 4 hours, followed by a continuous decrease in plasma volume.

Therefore, the effect of HAES-steril® 6% is a medium-term improvement of the plasma volume, haemodynamics and oxygen transport for at least 3 - 4 hours. At the same time disturbed microcirculation improves by improvement of haemorheology due to decreasing haematocrit, plasma viscosity and erythrocyte aggregation.

5.2 Pharmacokinetic properties

Absorption and distribution

HAES-steril 6% contains 6% HES 200/0.5 as colloidosmotically active ingredient. HES is metabolised in the serum by serum amylase. Due to a molecular weight of 200,000 D and a degree of molar substitution MS of 0.5 a persistence in the circulatory system over the medium-term is reached.

The HAES-steril® 6% concentration following infusion increases to 94% of the administered dose and decreases to 68, 42, 27 and 16 percent at 1, 3, 6, and 12 hours post infusion respectively.

HAES-steril® 6% is continuously hydrolysed by serum amylase and eliminated renally. After about 24 hours, approximately 47% of infused HAES-steril® 6% is recovered in the urine and shout 10% is still detectable in the serum.

5.3 Preclinical safety data

Toxicology

Acute toxicity

The LD_{50} for HES 200,000 in mice corresponds to a dose greater than 12 g/kg BW. This is equivalent to a human dose greater than 840 g HES in a 70 kg individual. This dose is greater than any dose that would reasonable be expected to be used in a clinical setting.

Subacute and subchronic toxicity

The subchronic toxicity was tested in various animals. An increasing dosage of up to 1.5 g HES/kg BW/day (≅ 25 ml HES 6%/kg BW/day***)*** in rabbits, 3 g HES/kg BW/day (≅ 50 ml HES 6%/kg BW/day) in mice and 4 g HES/kg BW/day (≅ 40 ml HES 10%/kg BW/day***)*** in dogs showed no irreversible or toxic effects on liver, spleen, lungs or lymph nodes, except for increased organ weight and temporary, histopathologically determined, vacuolar changes of the reticulo-endothelial-system (RES).

The above mentioned changes are typical for the administration of all exogenous colloids and therefore not specific for HAES-steril 6%.

Teratogenic potential

No teratogenic effects were found.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Hydroxide
Hydrochloric Acid
Water for Injections

6.2 Incompatibilities

Should mixing with other drugs be necessary, 100% hygienic injection, thorough mixing, and above all, compatibility must be ensured.

6.3 Shelf-life

a) Shelf-life of the medicinal product as packaged for sale

- 5 years in glass bottles
- 5 years in polyethylene containers (PE bottle)
- 3 years in **free***flex*® bags

b) Shelf-life after reconstitution according to directions

Not applicable

c) Shelf-life after first opening of the container

The product should be used immediately after opening.

6.4 Special precautions for storage

None

6.5 Nature and contents of container

Colourless glass bottle with halobutyl rubber closure and aluminium cap:
10 x 250ml; 10 x 500 ml

Polyolefine bag (Freeflex):
10 x 250 ml, 20 x 250 ml
10 x 500 ml, 15 x 500 ml;

Polyethylene bottle (Bottlepack):
10 x 250 ml, 10 x 500 ml

6.6 Instruction for use / handling

HAES-steril® 6% must not be used after expiry date!
Only use if the solution is clear and the container is undamaged!
Keep out of reach of children!

7. MARKETING AUTHORISATION HOLDER

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