Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Hemohes 10% w/v solution for infusion, Ecobag

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1000ml of solution contains:

Poly(0-2-hydroxyethyl) starch (HES)	100.0	g
Sodium Chloride	9.0	g

For excipients, see section 6.1.

Physico-chemical Properties:

Weight average molecular weight (Mw; Dalton)	200,000	
Number average molecular weight (Mn, Dalton)	~80,000	
Molar substitution (MS)	0.5 (0.45-0.55)	
Theoretical osmolarity	310	mOsm/l
pH	4.0 – 7.0	
Electrolytes:		
Sodium	154.0	mmol/litre
Chloride	154.0	mmol/litre

3 PHARMACEUTICAL FORM

Solution for Infusion
Clear colourless aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hemohes 10% is used as a colloidal plasma volume substitute in the following situations:

- Prevention and treatment of hypovolaemia (e.g., following shock due to haemorrhage or trauma, peri-operative blood loss, burns, sepsis).
- Prevention of hypotension (e.g., in connection with induction of general, spinal or peridural anaesthesia).
- Haemodilution.
- Extra-corporeal circulation.

4.2 Posology and method of administration

Total dosage, duration and rate of infusion will depend upon the amount of blood or plasma lost and the condition of the patient, and will need to be adjusted as necessary by monitoring the usual circulatory parameters (*e.g.* blood pressure). The risk of circulatory overload by too-rapid infusion or inappropriately large doses must be borne in mind especially with Hemohes 10%, which is hyperoncotic.

In order to detect the occurrence of an anaphylactoid reaction as early as possible, the first 20-30 ml of Hemohes should be infused slowly and under careful observation.

Maximum daily dosage:
A maximum daily dose of 2.0 g HES/kg/day should not be exceeded. This corresponds to 20 ml/kg/day of the 10% solution (=1,500 ml/day in a 75 kg-individual).

In the literature a correlation between dose and frequency of itching in patients with otoneurological disorders (e.g. tinnitus, sudden deafness) has been described. In such cases it is advisable to reduce the dose to 250 ml/day. This will reduce the risk of itching as a side effect.

Maximum infusion rate:
The maximum rate of infusion is dependent on the clinical situation. Patients with acute haemorrhagic shock may be administered up to 20 ml/kg/hr (equivalent to 0.33 ml/kg/min) and, in life-threatening situations, 500 ml as a rapid infusion (under pressure).

The rates of infusion selected for perioperative indications and for burns and septic shock patients will typically be lower.

Further Information:
Hemohes 10% is hyperoncotic. Infusion results in an initial dehydration of the extravascular compartment which must be compensated by infusion of a crystalloid solution.

Patients with primarily interstitial fluid losses first need to be administered a crystalloid. After infusion of Hemohes, serum ionogramme and fluid balance controls are required. Electrolytes are to be replaced as required. In all patients adequate fluid supply is essential. Renal function must be monitored during the infusion (control of serum creatinine).

Because of the possibility of allergic (anaphylactic/anaphylactoid) reactions, appropriate monitoring of patients is necessary.

4.3 Contraindications

- Known hypersensitivity to Hydroxyethyl Starch.
- Hypervolaemia.
- Hyperhydration (e.g., water intoxication).
- Congestive heart failure.
- Renal insufficiency.
- Severe blood coagulation disorders.

4.4 Special warnings and precautions for use

Anaphylactoid/*Anaphylactic* reactions: Hydroxyethyl starch (HES) solutions, like all commonly used colloidal plasma substitutes, may cause anaphylactoid reactions of variable severity, ranging from benign skin symptoms (urticaria) through flushing of the face and neck to the much less frequently occurring ones: fall in blood pressure, shock, bronchospasm, cardiac and respiratory arrest.
Such reactions can occur both in conscious and anaesthetised patients. However in the acute phase of volume deficiency shock, anaphylactoid reactions have never been observed.

There is no known test for advance identification of patients liable to experience anaphylactoid *or anaphylactic* reactions, nor can the course of such reactions be predicted. The pathomechanism of *these* reactions following infusion of HES solutions is as yet poorly understood. Prophylactic administration of corticosteroids has not proved useful.

General guidelines for the prevention and therapy of adverse reactions include:

- Adequate information should be available to physicians and nursing staff regarding the nature and severity of reactions attributable to colloidal plasma volume substitutes.
- Equipment and medicaments for resuscitation must be readily available.
- Careful observation of the patient during administration of the first 20 - 30 ml.
- The infusion must be stopped immediately at the first signs of an intolerance reaction. Treatment should be in response to the intensity of the reaction.

Haemodilution: Like all colloidal plasma substitutes, HES produces coagulation factor dilution. In particular, there is a change in Factor VIII activity, which is, however, temporary and reversible, and, in the absence of other blood coagulation disorders, has no clinical significance. Hemohes should be used with caution in patients with pre-existing blood coagulation disorders, chronic liver disease or haemorrhagic diathesis.

Haematocrit may be decreased and plasma proteins diluted by infusion of large volumes of Hemohes. If the haematocrit falls below 25 % (in patients at cardiovascular or pulmonary risk 30 %) packed red cells or full blood have to be given. Administration of albumin 20 %, fresh frozen plasma or platelets should also be considered if excessive dilution occurs.

Circulatory overload: The possibility of circulatory overload should be kept in mind, especially with hyperoncotic Hemohes 10% where plasma volume expands in excess of the volume infused. Cautions should be *taken in patients* at risk of pulmonary oedema and/or congestive heart failure.

Impaired renal clearance: Particular caution should be exercised and the dosage adjusted as appropriate in patients who have impaired renal clearance since this is the principal way in which Hemohes is eliminated. In these patients especially, adequate fluid supply is essential. Renal function must be monitored during infusion.

Pediatric use: The safety and effectiveness of Hemohes in children under 12 years of age has not been established.

Hypernatraemia: Hemohes should be used with caution in patients with hypernatraemia.

4.5 Interaction with other medicinal products and other forms of interaction

Emergency use in patients whose blood group is not known requires that blood samples for blood typing and determination of irregular agglutinins be drawn prior to infusion of large volumes of HES (to avoid false-positive results).

Elevated serum α-amylase concentrations about three times the upper limit of normal may be observed temporarily following administration of HES solutions. This elevated α-amylase activity is due to the formation of an enzyme-substrate complex of amylase and HES subject to slow renal elimination and therefore must not be considered diagnostic of impaired pancreatic function.

4.6 Pregnancy and lactation

Pregnancy: There is insufficient evidence of safe use in pregnant women. Animal studies have yielded evidence of embryotoxic/teratogenic effects of Hemohes 10% when given in doses more than twice the human dose. Hemohes should be used during pregnancy only if the potential benefits justify the potential risk to the foetus.

Lactation: There is as yet no experience with usage of this product in nursing mothers.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Anaphylactoid reactions can occur as a result of Hemohes infusion (*cf. 4.4. Special warnings and precautions).*

In a number of cases persistent, reversible itching has been reported after long-term administration and high cumulative doses. This pruritus may not appear until weeks after the last infusion and may persist over months.

4.9 Overdose

The main risk of an acute overdose would be volume overload. In this case infusion must be stopped immediately and administration of diuretics should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Hemohes 10% a hyperoncotic colloidal plasma volume substitute containing 10 % hydroxyethyl starch (HES) in normal saline (0.9 % sodium chloride). Its weight average molecular weight (Mw) is 200,000 Dalton and its Mn value (i.e., the average weight of its osmotically active particles) is about 80,000 Dalton.

The starting material for the manufacture of HES is the amylopectin portion of vegetable wax corn starch, which closely resembles the endogenous polysaccharide glycogen. The introduction of hydroxyethyl groups delays the intravascular cleavage of amylopectin by endogenous α-amylase. On average, Hemohes contains 5 hydroxyethyl groups per 10 glucose units, yielding a molar substitution (MS) of 0.5.

The duration of the plasma volume expanding action depends primarily on the MS and to a lesser extent on the Mw. Intravascular hydrolysis of the HES polymers continually releases smaller molecules, which, in turn, are oncotically active before being eliminated via the kidneys.

Like all semi-synthetic colloids, HES is subjected to partial, transient storage in RES cells in particular, but an adverse effect on function could not yet be demonstrated.

Hemohes 10% is hyperoncotic, i.e., plasma volume initially increases in excess of the volume infused (approximately 145 %).

Infusion of hypovolaemic patients with Hemohes normalises the circulating blood volume and improves haemodynamic, cardiac, and haemorrheological parameters. Blood volume is maintained for at least 4-6 hours.

5.2 Pharmacokinetic properties

Dependent on the rate of infusion and the mode of administration (iso-, hypervolaemic infusion) the initial elimination half-life from the serum is about 3 - 6 hours. Hemohes molecules smaller than about 50,000 Dalton are subject to rapid renal elimination by glomerular filtration. After single dosing with 500 ml about 50 % of the dose administered is recovered in the urine within 24 hours, at which point only about 10 % can still be detected in the serum. Serum HES levels fall to the limit of detection within 7-10 days after the infusion.

5.3 Preclinical safety data

Animal studies have yielded evidence of embryotoxic/teratogenic effects of Hemohes 10% (*cf. 4.6. Pregnancy and lactation*).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injections

6.2 Incompatibilities

Mixing with other drugs may produce incompatibilities. Therefore only mixtures with known compatibility should be prepared.

6.3 Shelf Life

Two years.
Shelf life after first opening: The product should be used immediately.

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

Polypropylene bag (Ecobag) with butyl rubber stopper and multiplayer outer bag.

1 x 20 plastic infusion bags of 500ml.
1 x 10 plastic infusion bags of 1000ml.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only.
Once opened, Hemohes should be used immediately.
Any portion of the contents remaining after use should be discarded.
Use only clear solutions, practically free from particles, from intact containers.

7 MARKETING AUTHORISATION HOLDER

B. Braun Melsungen AG
Carl-Braun-Strasse 1
D-34212 Melsungen
Germany

8 MARKETING AUTHORISATION NUMBER

PA 736/1/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 September 2005

10 DATE OF REVISION OF THE TEXT