VOLUVEN FRESENIUS

I. SUMMARY OF THE DOSSIER

I.B. SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

Voluven® Fresenius

6% Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1000 ml contain:

Poly(O-2-hydroxyethyl)starch (Molar substitution 0.38 - 0.45) (Mean molecular weight : 130,000)	60.00 g
Sodium chloride	9.00 g
Na^+ 154 mmol	
Cl^- 154 mmol	

Theoretical osmolarity	308 mosmol/l
pH	4.0 - 5.5
Titratable acidity	< 1.0 mmol NaOH/l

3. PHARMACEUTICAL FORM

Solution for infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Therapy and prophylaxis of hypovolaemia

4.2 Posology and method of administration

For continuous intravenous infusion.

The initial 10-20 ml are to be infused slowly, keeping the patient under close observation (due to possible anaphylactoid reactions).

The daily dose and rate of infusion depend on the patient's blood loss, on the maintenance or restoration of haemodynamics and on the haemodilution (dilution effect).

The maximum daily dose is 50 ml / kg b.w. / day.

Voluven® Fresenius can be administered repetitively over several days according to the patient's needs. The duration of treatment depends on the duration and extent of hypovolaemia, the haemodynamics and on the haemodilution.

There is currently limited experience with this maximum daily dose given for prolonged periods.

4.3 Contra-indications

- Fluid overload (hyperhydration) including pulmonary oedema
- Renal failure with oliguria or anuria
- Patients receiving dialysis treatment
- Intracranial bleeding
- Severe hypernatremia or severe hyperchloremia
- Known hypersensitivity to hydroxyethyl starches

4.4 Special warnings and special precautions for use

Fluid overload caused by overdose should be avoided in general. Particularly for patients with cardiac insufficiency or severe kidney dysfunctions the increased risk of hyperhydration must be taken into consideration; posology must be adapted.

In cases of severe dehydration a crystalloid solution should first be given.

Particular care must be taken in patients with severe liver disease or severe bleeding disorders, e.g. severe cases of von Willebrand´s disease.

It is important to supply sufficient fluid and to regularly monitor kidney function and fluid balance.

Serum electrolytes should be monitored.

There are no data available on the use of Voluven Fresenius in children. Voluven Fresenius may be given to children only after careful risk/benefit evaluation.

Regarding the occurence of anaphylactoid reactions please refer to section 4.8 “Undesirable effects”.

4.5 Interaction with other medicaments and other forms of interaction

No interactions with other drugs or nutritional products are known to date.

Please refer to section 4.8 “Undesirable effects“ concerning the concentration of serum amylase which can rise during administration of hydroxyethyl starch and can interfere with the diagnosis of pancreatitis.

4.6 Pregnancy and lactation

For Voluven Fresenius no clinical data on exposed pregnancies are currently available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or postnatal development (see section 5.3). No evidence of teratogenicity was seen.

Voluven Fresenius should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

There are currently no clinical data available on the use of Voluven Fresenius in lactating women.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Medicinal products containing hydroxyethyl starch may lead to anaphylactoid reactions (hypersensitivity, mild influenza-like symptoms, bradycardia, tachycardia, bronchospasm, non-cardiac pulmonary oedema) in very rare cases. In the event of an intolerance reaction occurring the infusion should be

discontinued immediately and the appropriate emergency medical treatment initiated.

The concentration of serum amylase can rise during administration of hydroxyethyl starch and can interfere with the diagnosis of pancreatitis.

Pruritus (itching) after prolonged administration of high dosages is a known undesirable effect of hydroxyethyl starches.

At high dosages the dilution effects may result in a corresponding dilution of blood components such as coagulation factors and other plasma proteins and in a decrease of hematocrit.

With the administration of hydroxyethyl starches disturbances of blood coagulation can occur depending on the dosage.

4.9 Overdose

As with all volume substitutes, overdose can lead to overloading of the circulatory system (e.g. pulmonary oedema). In this case the infusion should be stopped immediately and if necessary, a diuretic should be administered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: B05A A

Pharmacotherapeutic group: Plasma substitutes and plasma protein fractions.

Voluven Fresenius is an artificial colloid for volume replacement whose effect on intravascular volume expansion and haemodilution depends on the molar substitution by hydroxyethyl groups (0.4), the mean molecular weight (130.000 Da), the concentration (6%) as well as the dosage and infusion rate.

Infusion of 500 ml Voluven Fresenius in 30 minutes in volunteers results in a plateau-like non-expansive volume increase of approximately 100 % of the infused volume which lasts for approximately 4 to 6 hours.

Isovolaemic exchange of blood with Voluven Fresenius maintains blood volume for at least 6 hours.

5.2 Pharmacokinetic properties

The pharmacokinetics of hydroxyethyl starch is complex and depends on the molecular weight and mainly on the molar substitution degree. When applied intravenously, molecules smaller than the renal threshold (60,000-70,000 Da) are readily excreted in the urine while larger ones are metabolised by plasma α-amylase before the degradation products are renally excreted.

The mean *in vivo* molecular weight of Voluven Fresenius in the plasma is 70,000 – 80,000 Da immediately after infusion and remains above the renal threshold throughout the therapeutic period.

The volumen of distribution is about 5.9 litres. Within 30 minutes of infusion the plasma level of Voluven Fresenius is still 75% of the maximum concentration. After 6 hours the plasma level has decreased to 14%. Following a single dose of 500 ml hydroxyethyl starch plasma levels almost return to baseline after 24 hours.

Plasma clearance was 31.4 ml/min when 500 ml of Voluven Fresenius was administered, with an AUC of 14.3 mg/ml h, which shows a non-linear pharmacokinetic. Plasma half-lives were t 1/2α = 1.4 h and t 1/2ß = 12.1 h when 500 ml were administered on a single occasion.

Using the same dose [500ml] in subjects with stable mild to severe renal impairment, the AUC moderately increased by a factor of 1.7 (95% confidence limits 1.44 and 2.07) in subjects with Cl_{Cr} < 50 ml/min compared to > 50 ml/min. Terminal half life and peak HES concentration were not affected by renal impairment. At Cl_{Cr} => 30 ml/min, 59% of the drug could be retrieved in the urine, vs 51 % at Cl_{Cr} 15 to 30 ml/min.

No significant plasma accumulation occurred even after a daily administration of 500 ml of a 10% solution to volunteers containing HES 130/0.4 over a period of 10 days. In an experimental model in rats using repetitive doses of 0.7g/kg BW per day of Voluven Fresenius over 18 days, 52 days after the last administration tissue storage was 0.6% of the total administered dose.
There are no data available for the use of Voluven Fresenius in dialysis.

5.3 Preclinical safety data

Subchronic toxicity:

The intravenous infusion of 9 g of the hydroxyethyl starch contained in Voluven Fresenius/kg b.w./day in rats and dogs for 3 months resulted in no signs of toxicity, except for a toxicity from the increased workload on the kidney and the liver, uptake and metabolism of hydroxyethyl starch in the reticulo-endothelial system, hepatic parenchyma, and other tissues associated with the animals´ unphysiological state during the test period.

The lowest toxic dose is above 9 g of the hydroxyethyl starch contained in Voluven Fresenius/kg b.w./day, which is at least 3 times greater than maximum human therapeutic dose levels.

Reproductive toxicity:

The type of hydroxyethyl starch present in Voluven Fresenius had no teratogenic properties in rats or rabbits. Embryolethal effects were observed in rabbits at 50 ml/kg BW/day. In rats, bolus injection of this dose during pregnancy and lactation reduced body weight of offspring and induced developmental delays. Signs of fluid overloading were seen in the dams. Fertility studies on directly exposed animals have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide

Hydrochloric acid

Water for injections

6.2 Incompatibilities

The mixing with other drugs should be avoided. If, in exceptional cases, a mixture with other drugs is required, care should be taken with the compatibility (clouding or precipitation), hygienic injection and a good admixture.

6.3 Shelf life

a) Shelf life of the product as packaged for sale:

Glass bottle: 3 years
Freeflex bag: 3 years
PVC bag: 2 years

b) Shelf life after dilution or 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

Do not freeze

6.5 Nature and contents of container

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

Polyolefine bag (Freeflex)	
with overwrap	10 x 250 ml, 20 x 250 ml 10 x 500 ml, 15 x 500 ml;
without overwrap	40 x 250 ml, 20 x 500 ml
PVC bag	25 x 250 ml, 15 x 500 ml

6.6 Instructions for use/handling

To be used immediately after the bottle or bag is opened.

Do not use Voluven Fresenius after expiry date. Any unused solution should be discarded.

Use only clear solutions and undamaged containers.

Keep out of reach of children

7. MARKETING AUTHORISATION HOLDER

Name or style and permanent address or registered place of business of the holder of the marketing authorisation

Varies from country to country

8. MARKETING AUTHORISATION NUMBER

Varies from country to country

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Varies from country to country

10. DATE OF (PARTIAL) REVISION OF THE TEXT

May 2002