SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Voluven 6% solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1000 ml solution for infusion contain:

Poly(O-2-hydroxyethyl)starch	60.00 g
- Molar substitution: 0.38 - 0.45	
- Mean molecular weight: 130,000 Da	
Sodium chloride	9.00 g
Electrolytes:	
Na^+	154 mmol
Cl^-	154 mmol
Theoretical osmolarity	308 mosmol/l
pH	4.0 - 5.5
Titratable acidity	< 1.0 mmol NaOH/l

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for infusion

A clear to slightly opalescent solution, colourless to slightly yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Voluven 6% is indicated for the treatment and prophylaxis of hypovolaemia in adults and children. It is not a substitute for red blood cells or coagulation factors in plasma.

4.2 Posology and method of administration

Voluven 6% is administered by intravenous infusion only.

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). Voluven 6% can be administered repetitively over several days.

The initial 10 to 20 ml should be infused slowly, keeping the patient under close observation due to possible anaphylactic/anaphylactoid reactions.

Adult dose:

Up to 50 ml of Voluven 6% per kg of body weight per day (equivalent to 3.0 g hydroxyethyl starch and 7.7 mEq sodium per kg of body weight). This dose is equivalent to 3,500 mL Voluven 6% for a 70 kg patient.

Paediatric dose:

The dosage in children should be adapted to the individual patient colloid needs, taking into account the disease state, as well as the haemodynamic and hydration status (see section 5.1).

In 41 newborns to infants (< 2 years), a mean dose of 16 ± 9 ml/kg was administered. In 31 children from 2 – 12 years of age a mean dose of 36 ± 11 ml/kg was administered. The dose in adolescents > 12 is the same as the adult dose.

4.3 Contraindications

Do not use HES products in:

- patients with sepsis
- patients with severe liver disease
- patients with known hypersensitivity to hydroxyethyl starch
- clinical conditions where volume overload is a potential problem, especially in cases of pulmonary oedema and congestive cardiac failure
- patients with pre-existing coagulation or bleeding disorders
- patients with renal failure with oliguria or anuria not related to hypovolaemia
- patients receiving dialysis treatment
- patients with severe hypernatraemia or severe hyperchloraemia
- patients with intracranial bleeding

4.4 Special warnings and precautions for use

In critically ill patients, crystalloids should be used primarily, and HES products should only be used, if crystalloids are not sufficient to stabilise the patient, and if the anticipated benefit justifies the risk.

Anaphylactic/anaphylactoid reactions (hypersensitivity, mild influenza-like symptoms, bradycardia, tachycardia, bronchospasm, non-cardiac pulmonary oedema) have been reported with solutions containing hydroxyethyl starch. If a hypersensitivity reaction occurs, administration of the drug should be discontinued immediately and the appropriate treatment and supportive measures should be undertaken until symptoms have resolved (see section 4.8).

Avoid use in patients with pre-existing renal dysfunction.

Discontinue use of Voluven 6% at the first sign of clinically relevant renal injury.

Continue to monitor renal function in hospitalised patients for at least 90 days as use of renal replacement therapy has been recorded up to 90 days after administration of HES products.

Monitor the coagulation status in patients undergoing open heart surgery in association with cardiopulmonary bypass as excess bleeding has been reported with other HES solutions in this population. Discontinue the use of Voluven 6% at the first sign of clinically relevant coagulopathy.

Avoid fluid overload; adjust dosage in patients with cardiac or renal dysfunction.

Fluid status and rate of infusion should be assessed regularly during treatment, especially in patients with cardiac insufficiency or severe kidney dysfunction.

In cases of severe dehydration a crystalloid solution should be given first. Generally, sufficient fluid should be administered in order to avoid dehydration.

Particular care must be taken in patients with electrolyte abnormalities.

Clinical evaluation and periodic laboratory determinations are necessary to monitor fluid balance, serum electrolyte concentrations, kidney function, acid-base balance, and coagulation parameters during prolonged parenteral therapy or whenever the patient's condition warrants such evaluation. Monitor liver function in patients receiving HES products, including Voluven 6%.

4.5 Interaction with other medicinal products and other forms of interaction

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

Elevated serum amylase levels may be observed temporarily following administration of the product and can interfere with the diagnosis of pancreatitis.

At high dosages the dilutional effects may result in decreased levels of coagulation factors and other plasma proteins and a decrease in haematocrit.

4.6 Pregnancy and lactation

There are limited clinical study data available from the use of a single dose of Voluven¯6% in pregnant women undergoing caesarean section with spinal anaesthesia. No negative influence of Voluven 6% on patient safety could be detected; a negative influence on the neonate could also not be detected (see section 5.1).

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 6% should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Information on the use of Voluven 6% during labour or delivery is unknown with the exception of caesarean section (see above). Use if clearly needed.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Voluven 6% is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

Voluven 6% has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The undesirable effects are defined as follows: *Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), frequency not known (cannot be estimated from the available data)*

Blood and lymphatic system disorders:

Rare (in high doses): With the administration of hydroxyethyl starch disturbances of blood coagulation beyond dilution effects can occur depending on the dosage.

Immune system disorders:

Rare: Medicinal products containing hydroxyethyl starch may lead to anaphylactic/anaphylactoid reactions (hypersensitivity, mild influenza-like symptoms, bradycardia, tachycardia, bronchospasm, non-cardiac pulmonary oedema). If a hypersensitivity reaction occurs, administration of the drug should be discontinued immediately and the appropriate treatment and supportive measures should be undertaken until symptoms have resolved.

Skin and subcutaneous tissue disorders:

Common (dose dependent): Prolonged administration of high dosages of hydroxyethyl starch may cause pruritus (itching) which is a known undesirable effect of hydroxyethyl starches.

Investigations:

Common (dose dependent): The concentration of serum amylase can rise during administration of hydroxyethyl starch and can interfere with the diagnosis of pancreatitis. The elevated amylase is due to the formation of an enzyme-substrate complex of amylase and hydroxyethyl starch subject to slow elimination and must not be considered diagnostic of pancreatitis.

Common (dose dependent): 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 haematocrit.

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 A07

Pharmacotherapeutic group: Plasma substitutes and plasma protein fractions.

The active ingredient hydroxyethyl starch 130/0.4 is a derivative of waxy maize starch mainly consisting of a glucose polymer (amylopectin) predominately composed of α-1,4-connected glucose units with several α-1,6-branches. Voluven 6% is an artificial colloid for volume replacement. Its pharmacological properties depend on the molar substitution by hydroxyethyl groups (0.4), the mean molecular

weight (130,000 Da), the concentration (6%), the substitution ratio (C_2/C_6 ratio) of approximately 9:1 as well as the dosage and infusion rate. To describe the molecular weight and molar substitution characteristics of the hydroxyethyl starch in Voluven 6%, the compound is designated as hydroxyethyl starch 130/0.4. The low molar substitution, medium molecular weight, and narrow molecular weight distribution of HES 130/0.4 contained in Voluven 6% contribute to its beneficial effects on pharmacokinetics and intravascular volume effect.

Infusion of 500 ml Voluven 6% 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 6% maintains blood volume for at least 6 hoursPaediatric use

In one trial, newborns and infants < 2 years of age undergoing elective surgery were randomised to receive Voluven 6% (N=41) or 5% albumin (N=41). The mean dose of Voluven 6% administered was 16 ± 9 ml/kg.

In an additional trial, children from 2 – 12 years of age undergoing cardiac surgery were randomised to receive Voluven 6% (N=31) or 5% albumin (N=30). The mean dose administered was 36 ± 11 ml/kg.

Use of Voluven 6% in adolescents > 12 years is supported by evidence from adequate and well-controlled studies of Voluven 6% in adults.

Dosage in children should be adapted to individual patient colloid needs, taking into account underlying disease, haemodynamics, and hydration status (see section 4.2).

Treatment of pregnant women undergoing caesarian section

There are limited clinical study data available from the use of a single dose of Voluven 6% in pregnant women undergoing caesarean section with spinal anaesthesia. The occurrence of hypotension was significantly lower for Voluven 6% in combination with crystalloid compared to crystalloid control alone (36.6% vs. 55.3%). Overall, efficacy evaluation showed significant benefits for Voluven 6% in the prevention of hypotension and in the occurrence of severe hypotension compared to crystalloid control.

5.2 Pharmacokinetic properties

The pharmacokinetics of hydroxyethyl starch is complex and depends on the molecular weight and mainly on the molar substitution degree and the substitution pattern (C_2/C_6 ratio). 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 6% in the plasma is 70,000 – 80,000 Da immediately after infusion and remains above the renal threshold throughout the therapeutic period.

The volume of distribution is about 5.9 litres. Within 30 minutes of infusion the plasma level of Voluven 6% 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 6% was administered, with an AUC of 14.3 mg/ml h, which shows a non-linear pharmacokinetic. Plasma half-lives were $t_{1/2\alpha}$ = 1.4 h and $t_{1/2ß}$ = 12.1 h when 500 ml were administered on a single occasion.

Using the same dose (500 ml) 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. Plasma levels of Voluven 6% almost returned to baseline levels 24 hours following infusion.

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 6% over 18 days, 52 days after the last administration tissue storage was 0.6% of the total administered dose.

In a further pharmacokinetic study, eight stable patients with end stage renal disease (ESRD) received a single dose of 250 ml (15 g) of HES 130/0.4 (6%.).3.6 g (24%)

of the HES dose was eliminated during a 2-hour haemodialysis session (500 mL dialysate per minute, Filter HD Highflux FX 50, Fresenius Medical Care, Germany). After 24 hours the mean HES plasma concentration was 0.7 mg/ml. After 96 hours the mean plasma concentration of HES was 0.25 mg/ml. HES 130/0.4 (6%) is contraindicated in patients receiving dialysis treatment (see section 4.3).

Pharmacokinetic data in patients with hepatic insufficiency or in paediatric or geriatric patients are not available. Effects of gender on the pharmacokinetics of Voluven 6% have not been studied.

5.3 Preclinical safety data

Repeat dose toxicity:

Three-month repeat infusion toxicology studies were conducted in rats and dogs in which three groups of animals were administered daily intravenous infusion over three hours. Dosing volumes of either 60 or 90 ml/kg body weight of HES 130/0.4 (10% solution) or 90 ml/kg 0.9% sodium chloride injection were studied. Observed toxicity following repeat infusion of hydroxyethyl starch is consistent with the oncotic properties of the solution resulting in hypervolaemia in the animals. No HES specific toxicity was detected up to doses of 9 g/kg which is at least 3 times the human dose. There were no gender-related effects on toxicity following repeat administration of HES 130/0.4 in rats or dogs.**Mutagenesis and carcinogenesis:**No mutagenic effects were observed with HES 130/0.4 (10%) solution in the following tests on mutagenic activity: *Salmonella typhimurium* reverse mutation assay (*in vitro*), mammalian cells in the *in vitro* gene mutation assay, assessment of the clastogenic activity in cultured human peripheral lymphocytes (*in vitro)*, bone marrow cytogenetic test in Sprague-Dawley rats. Long-term studies in animals to evaluate the carcinogenic potential of HES 130/0.4 (10%) in 0.9% sodium chloride solution have not been performed.

Reproductive toxicity:

In reproduction studies in rats and rabbits, HES 130/0.4 (10% solution) had no teratogenic properties. Embryo-foetotoxicity in rats and rabbits was only observed at maternal-toxic dose levels. Embryolethal effects were observed in rabbits at 5 g/kg body weight/day. In rats, bolus injection of this dose during pregnancy and lactation reduced body weight of offspring and induced developmental delays. Signs of fluid overload were seen in the dams. HES 130/0.4 (10% solution) had no effect in studies assessing skin sensitization, antigenicity, and blood compatibility.

In a rat fertility study no influence on male and female fertility parameters were observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

Water for injection

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:

free*flex* bag: 3 years

b) 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.
Do not store above 25°C.

6.5 Nature and contents of container

Polyolefine bag (**free***flex*) with overwrap
10 x 250 ml, 20 x 250 ml, 30 x 250 ml,
35 x 250 ml, 40 x 250 ml
10 x 500 ml, 15 x 500 ml, 20 x 500 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only

To be used immediately after the bottle is opened.

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

Any unused solution should be disposed of in accordance with local requirements.

Use only clear, particle-free solutions and undamaged containers.

Remove the overwrap from the Polyolefine (**free***flex)* bag prior to use.

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