SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Volulyte 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 acetate trihydrate 4.63 g
- Sodium chloride 6.02 g
- Potassium chloride 0.30 g
- Magnesium chloride hexahydrate 0.30 g

Electrolytes:

- Na⁺ 137.0 mmol/l
- K⁺ 4.0 mmol/l
- Mg²⁺ 1.5 mmol/l
- Cl⁻ 110.0 mmol/l
- CH₃COO⁻ 34.0 mmol/l

Theoretical osmolarity: 286.5 mosm/l
Titratable acidity: < 2.5 mmol NaOH/l
pH: 5.7 – 6.5

For a 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

Therapy and prophylaxis of hypovolaemia. Maintenance of adequate circulating blood volume during surgical procedures.

4.2 Posology and method of administration

For intravenous use as 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 depends on the patient’s blood loss, on the maintenance or restoration of haemodynamics and on the haemodilution (dilution effect).

Maximum daily dose:
Up to 50 ml of Volulyte per kg of body weight (equivalent to 3.0 g hydroxyethyl starch, 6.85 mmol sodium and 0.2 mmol potassium per kg of body weight). This is equivalent to 3,500 mL Volulyte for a 70 kg patient.

Volulyte 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 and shock, the haemodynamics and on the haemodilution.

For the dosage in critically ill patients please refer to section 4.4.

Treatment of children
Regarding the use in children please see section 5.1.

The dosage in children should be adapted to the individual patient colloid needs, taking into account basic disease, haemodynamics, urine production and hydration status.

For handling instructions please refer to section 6.6.
4.3 Contraindications

- **Sepsis**

- **Severe liver disease**

- Fluid overload (hyperhydration), especially in cases of pulmonary oedema and congestive cardiac failure

- Renal failure with oliguria or anuria not related to hypovolemia

- Patients receiving dialysis treatment

- Intracranial bleeding

- 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.

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

*In critically ill patients, dose reduction should be considered depending on the actual needs of the patient and the severity of the patient’s condition. The lowest possible effective dose should be given.*

Particular care must be taken in patients with severe electrolyte abnormalities, like hyperkalaemia, hypernatraemia, hypermagnesaemia and hyperchloraemia.

In metabolic alkalosis and clinical situations where alkalisation should be avoided, saline based solutions like a similar product containing HES 130/0.4 in 0.9% sodium chloride solution should be preferred over alkalising solutions like Volulyte.

It is important to supply sufficient fluid and to regularly monitor kidney function and fluid balance.
Particular care must be taken in patients with severe liver disease or severe bleeding disorders, e.g. severe cases of von Willebrand’s disease.

Serum electrolytes should be monitored.

No clinical trials have been performed with the product in children. The product may be used in children after careful benefit/risk evaluation (in particular in children below one year of age who independently of the product have a potential to develop lactic acidosis).

Regarding the occurrence of anaphylactoid reactions please refer to section 4.8.

4.5 Interaction with other medicinal products and other forms of interaction

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

Consideration should be given to the concomitant administration of medicinal products that can cause potassium or sodium retention.

Please refer to section 4.8 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 Volulyte no clinical data on exposed pregnancies are available.

There are limited clinical study data available from the use of a single dose of HES 130/0.4 (6%) in pregnant women undergoing caesarean section with spinal anesthesia. No negative influence of HES 130/0.4 (6%) in 0.9% sodium chloride on patient safety could be detected; a negative influence on the neonate could also not be detected (see section 5.1).

Animal studies with a similar product containing HES 130/0.4 in 0.9% sodium chloride solution do not indicate harmful effects with respect to pregnancy, embryo/fetal development, parturition or postnatal development (see section 5.3). No evidence of teratogenicity was seen.

Volulyte should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
It is unknown whether hydroxyethyl starch is excreted in human breast milk. The excretion of hydroxyethyl starch in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Volulyte should be made taking into account the benefit of breast-feeding to the child and the benefit of Volulyte therapy to the woman.

4.7 Effects on ability to drive and use machines

Volulyte has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The undesirable effects are divided into: 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)

Blood and lymphatic system disorders

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

Immune system disorders

Rare: Medicinal products containing hydroxyethyl starch may lead to anaphylactoid reactions (hypersensitivity, mild influenza-like symptoms, bradycardia, tachycardia, bronchospasm, non-cardiac pulmonary oedema). In the event of an intolerance reaction occurring the infusion should be discontinued immediately and the appropriate emergency medical treatment initiated.

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. The itching may not appear until weeks after the last infusion and may persist for months.

Investigations

Common (dose dependent): The concentration of serum amylase level 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 hematocrit.

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**

Pharmacotherapeutic group: Plasma substitutes and plasma protein fractions, ATC code: B05AA07.

Volulyte 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. Hydroxyethyl starch (130/0.4) contained in Volulyte is derived from waxy maize starch and has a substitution pattern ($C_2/C_6$ ratio) of approximately 9:1.

Infusion of 500 ml of a similar product containing HES 130/0.4 (6%) in 0.9% sodium chloride solution 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 HES 130/0.4 in 0.9% sodium chloride solution maintains blood volume for at least 6 hours.
Volulyte contains the electrolytes sodium ($\text{Na}^+$), potassium ($\text{K}^+$), magnesium ($\text{Mg}^{++}$), chloride ($\text{Cl}^-$) and acetate ($\text{CH}_3\text{COO}^-$) in an isotonic composition. Acetate is a metabolisable anion which is oxidised in different organs and has an alkalising effect.

Volulyte contains a reduced amount of chloride and therefore counteracts the development of hyperchloremic metabolic acidosis, especially when large dose infusions are required or in patients at risk for the development of metabolic acidosis.

In cardiac surgery, chloride levels were significantly lower and base excess levels were seen to be less negative for Volulyte in comparison to HES 130/0.4 (6%) in 0.9% sodium chloride solution.

Treatment of children
No clinical trials with the product in children have been performed. However, limited clinical data on the use of a similar product containing HES 130/0.4 (6%) in 0.9% sodium chloride solution in children is available. In non-cardiac surgery in 41 children including newborns to infants (< 2 years), a mean dose of $16 \pm 9 \text{ ml/kg}$ was administered safely and well tolerated for stabilisation of haemodynamics. The tolerability of this product administered perioperatively was comparable to 5% albumin (see section 4.2 and 4.4).

Treatment of pregnant women undergoing caesarean section
There are limited clinical study data available from the use of a single dose of HES 130/0.4 (6%) in 0.9% sodium chloride in pregnant women undergoing caesarean section with spinal anesthesia. The occurrence of hypotension was significantly lower for HES 130/0.4 (6%) compared to crystalloid control (36.6% vs. 55.3%). Overall efficacy evaluation showed significant benefits for HES 130/0.4 (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 $\alpha$-amylase before the degradation products are renally excreted.

The mean *in vivo* molecular weight of HES 130/0.4 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 HES 130/0.4 (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 HES 130/0.4 (6%) was administered, with an AUC of 14.3 mg/ml x h, which shows a non-linear pharmacokinetic. Plasma half-lives were $t_{1/2\alpha} = 1.4$ h and $t_{1/2\beta} = 12.1$ 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$_{Cr}$ $\geq$ 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 HES 130/0.4 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) requiring haemodialysis received a single dose of 250 ml (15g) of HES 130/0.4 (6%).

3.6 g (24%) of the HES dose was eliminated during a 2-hour hemodialysis 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
1.3.1 SPC, Labelling and Package Leaflet (Volulyte 6% Solution for Infusion)

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).

5.3 Preclinical safety data

Subchronic toxicity:

The intravenous infusion of 9 g of the hydroxyethyl starch contained in Volulyte/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/kg b.w./day of the hydroxyethyl starch contained in Volulyte, which is at least 3 times greater than maximum human therapeutic dose levels.

Reproductive toxicity:

The type of hydroxyethyl starch present in Volulyte had no teratogenic properties in rats or rabbits. Embryolethal effects were observed in rabbits at 5 g/kg BW/day. In rats, bolus injection of this dose during pregnancy and lactation reduced body weight of offspring and induced developmental delays. However, embryo-fetotoxicity in rats and rabbits was only observed at maternal-toxic dose levels. 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 (for pH adjustment)

Hydrochloric acid (for pH adjustment)
1.3.1 SPC, Labelling and Package Leaflet (Volulyte 6% Solution for Infusion)

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

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

Glass bottle: 4 years
freeflex 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

This medicinal product does not require any special storage conditions. Do not freeze.

6.5 Nature and contents of container

Colourless type II glass bottle with halobutyl rubber closure and aluminium cap:
1 x 250 ml, 10 x 250 ml; 1 x 500 ml, 10 x 500 ml

Polyolefin bag (freeflex)

with overwrap: 1 x 250 ml, 20 x 250 ml, 30 x 250 ml, 35 x 250 ml, 40 x 250 ml
1 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 or bag is opened.

Any unused solution should be discarded.

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

Remove the overwrap from the Polyolefin (free/lex) bag prior to use.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

Varies from country to country.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 2008-05-15

Date of last renewal: NA

10. DATE OF (PARTIAL) REVISION OF THE TEXT

December 2012 June 2013