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
Mg^{++}	1.5 mmol/l
Cl –	110.0 mmol/l
CH_3COO^-	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

Volulyte 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

Volulyte is administered by intravenous infusion only.
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). Volulyte 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 Volulyte per kg of body weight per day (equivalent to 3.0 g hydroxyethyl starch, 6.85 mEq sodium and 0.2 mEq potassium per kg of body weight). This dose is equivalent to 3,500 mL Volulyte for a 70 kg patient.

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

4.3 Contraindications

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

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.
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.

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 Volulyte 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 Volulyte 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.

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.

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 Volulyte.

4.5 Interaction with other medicaments 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.
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

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 0.9% sodium chloride in pregnant women undergoing caesarean section with spinal anaesthesia.

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/foetal 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 foetus.
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 Volulyte is administered to a nursing 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 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. 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 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: B05AA07.
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. Volulyte 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 (C2/C6 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 Volulyte, 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 Volulyte contribute to its beneficial effects on pharmacokinetics, intravascular volume effect and haemodilution.

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 (Na^+), potassium (K^+), magnesium (Mg^{++}), chloride (Cl^-) and acetate (CH_3COO^-) 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 hyperchloraemic 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.

Paediatric use

No clinical trials have been performed with the product in paediatric patients. However, clinical data on the use of a similar product containing HES 130/0.4 (6%) in 0.9% sodium chloride solution in paediatric patients is available.

In one trial with a similar product containing HES 130/0.4 (6%) in 0.9% sodium chloride solution newborns and infants < 2 years of age undergoing elective surgery were randomised to receive HES 130/0.4 in 0.9% sodium chloride (N=41) or 5% albumin (N=41). The mean dose of HES 130/0.4 in 0.9% sodium chloride administered was 16 ± 9 ml/kg.

In an additional trial, children from 2 – 12 years of age undergoing cardiac surgery were randomised to receive HES 130/0.4 in 0.9% sodium chloride (N=31) or 5% albumin (N=30). The mean dose administered was 36 ± 11 ml/kg.

Studies conducted in children with HES 130/0.4 (6%) in 0.9% sodium chloride have not been of sufficient size or follow-up duration to assess the risks of renal injury and mortality in this patient population. The product may be given to 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) taking into account the disease state, as well as the haemodynamics and hydration status (see section 4.2).

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 (C2/C6 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 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 1/2ß = 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 $Cl_{Cr} \geq$ 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 HES 130/0.4 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 0.7 g/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.

There are limited data available for a similar product containing HES 130/0.4 (6%) in 0.9% sodium chloride solution in dialysis; however, HES 130/0.4 (6%) is contraindicated in patients receiving dialysis treatment.

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

5.3 Preclinical safety data

All non-clinical safety studies have been performed with a similar product containing HES 130/0.4 (10%) in 0.9% sodium chloride solution.

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.

Fertility studies on directly exposed animals with Volulyte have not been conducted. However, HES 130/0.4 (10%) solution in 0.9% sodium chloride did not impair fertility in male and female rats at IV doses of up to 5 g/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

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:	4 years
Freeflex bag:	3 years
KabiPac:	4 years

b) *Shelf life after first opening of the container:*

The product should be used immediately after opening.

6.4 Special precautions for storage

Store at or below 30°C.
Do not freeze.

6.5 Nature and contents of container

Colourless type II glass bottle with halobutyl rubber closure and aluminium cap:	10 x 250 ml; 10 x 500 ml
Polyolefine bag (freeflex) with overwrap	20 x 250 ml, 30 x 250 ml 35 x 250 ml, 40 x 250 ml 15 x 500 ml, 20 x 500 ml
PE bottle (KabiPac)	10 x 250 ml, 20 x 250 ml, 30 x 250 ml 10 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 Polyolefine (**free***flex*) bag prior to use.

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

7. MARKETING AUTHORISATION HOLDER

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8. DATE OF (PARTIAL) REVISION OF THE TEXT

March 2015

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