

## Summary of Product Characteristics



This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

### 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 (Ph.Eur.) | 60.00 g |
| - Molar substitution 0.38 – 0.45       |         |
| - Mean molecular weight = 130,000 Da   |         |
| (manufactured from waxy maize starch)  |         |
| Sodium acetate trihydrate              | 4.63 g  |
| Sodium chloride                        | 6.02 g  |
| Potassium chloride                     | 0.30 g  |
| Magnesium chloride hexahydrate         | 0.30 g  |

Electrolytes:

|                                  |              |
|----------------------------------|--------------|
| Na <sup>+</sup>                  | 137.0 mmol/l |
| K <sup>+</sup>                   | 4.0 mmol/l   |
| Mg <sup>++</sup>                 | 1.5 mmol/l   |
| Cl <sup>-</sup>                  | 110.0 mmol/l |
| CH <sub>3</sub> COO <sup>-</sup> | 34.0 mmol/l  |

|                         |                   |
|-------------------------|-------------------|
| Theoretical osmolarity: | 286.5 mosm/l      |
| Titration 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

Treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient (see sections 4.2, 4.3 and 4.4).

#### 4.2 Posology and method of administration

For intravenous use as infusion.

**Use of HES should be restricted to the initial phase of volume resuscitation with a maximum time interval of 24 h.**

The first 10-20 ml should be infused slowly and under careful monitoring of the patient so that any anaphylactic/anaphylactoid reaction can be detected as early as possible.

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).

The maximum daily dose is 30 ml/kg for Volulyte.

The lowest possible effective dose should be applied. Treatment should be guided by continuous haemodynamic monitoring so that the infusion is stopped as soon as appropriate haemodynamic goals have been achieved. The maximum recommended daily dose must not be exceeded.

Paediatric population:

Data are limited in children, therefore it is recommended not to use HES products in this population.

For handling instructions please refer to section 6.6.

### **4.3 Contraindications**

- Hypersensitivity to the active substances or to any of the other excipients listed in section 6.1
- Sepsis
- Burns
- Renal impairment or renal replacement therapy
- Intracranial or cerebral haemorrhage
- Critically ill patients (typically admitted to the intensive care unit)
- Hyperhydration
- Pulmonary oedema
- Dehydration
- Severe hyperkalaemia
- Severe hypernatraemia or severe hyperchloraemia
- Severely impaired hepatic function
- Congestive heart failure
- Severe coagulopathy
- Organ transplant patients

#### 4.4 Special warnings and precautions for use

Because of the risk of allergic (anaphylactic/anaphylactoid) reactions, the patient should be monitored closely and the infusion instituted at a low rate (see section 4.8).

**Surgery and trauma:**

There is a lack of robust long term safety data in patients undergoing surgical procedures and in patients with trauma. The expected benefit of treatment should be carefully weighed against uncertainty with regard to this long term safety. Other available treatment options should be considered.

The indication for volume replacement with HES has to be considered carefully, and haemodynamic monitoring is required for volume and dose control. (see also section 4.2)

Volume overload due to overdose or too rapid infusion must always be avoided. The dosage must be adjusted carefully, particularly in patients with pulmonary and cardiocirculatory problems. Serum electrolytes, fluid balance and renal function should be monitored closely.

HES products are contraindicated in patients with renal impairment or renal replacement therapy (see section 4.3). The use of HES must be discontinued at the first sign of renal injury.

An increased need for renal replacement therapy has been reported up to 90 days after HES administration. Monitoring of renal function in patients is recommended for at least 90 days.

Particular caution should be exercised when treating patients with impaired hepatic function or in patients with blood coagulation disorders.

Severe haemodilution resulting from high doses of HES solutions must also be avoided in the treatment of hypovolaemic patients.

In the case of repeated administration, blood coagulation parameters should be monitored carefully.

Discontinue the use of HES at the first sign of coagulopathy.

In patients undergoing open heart surgery in association with cardiopulmonary bypass the use of HES products is not recommended due to the risk of excess bleeding.

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

In metabolic alkalosis and clinical situations where alkalinisation 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 alkalinising solutions like Volulyte.

Paediatric population:

Data are limited in children, therefore it is recommended not to use HES products in this population (see section 4.2)

#### 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 Fertility, pregnancy and lactation

### Fertility

There are no data on the effects of Volulyte on human fertility. At human therapeutic doses animal studies do not indicate harmful effects with respect to fertility, however, alterations in fertility have been observed at maternal toxic dose (see section 5.3)

### Pregnancy

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 130.04 (6%) in pregnant women undergoing Caesarean section with spinal anaesthesia. 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 Volulyte should be used during early pregnancy only if the potential benefit justifies the potential risk to the foetus.

### Breast-feeding

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* ( $\geq 1/10$ ), *common* ( $\geq 1/100$  to  $< 1/10$ ), *uncommon* ( $\geq 1/1,000$  to  $< 1/100$ ), *rare* ( $\geq 1/10,000$  to  $< 1/1,000$ ), *very rare* ( $< 1/10,000$ ), *frequency not known* (cannot be estimated from available data)

### *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 anaphylactic/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 haematocrit.

*Hepatobiliary disorders*

*Frequency not known (cannot be estimated from the available data):* Hepatic injury

*Renal and urinary disorders*

*Frequency not known (cannot be estimated from the available data):* Renal injury

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: [www.hpra.ie](http://www.hpra.ie); E-mail: [medsafety@hpra.ie](mailto:medsafety@hpra.ie).

**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 manufactured from waxy maize starch and has a substitution pattern ( $C_2/C_6$  ratio) of approximately 8-12.

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<sub>3</sub>COO<sup>-</sup>) in an isotonic composition. Acetate is a metabolisable anion which is oxidised in different organs and has an alkalisising 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 population:

Data are limited in children, therefore it is recommended not to use HES products in this population.

#### Treatment of pregnant women undergoing Caesarian 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 anaesthesia. 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<sub>2</sub>/C<sub>6</sub> 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 non-linear pharmacokinetics. 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<sub>Cr</sub> < 50 ml/min compared to > 50 ml/min.

Terminal half life and peak HES concentration were not affected by renal impairment. At Cl<sub>Cr</sub> ≥ 30 ml/min, 59% of the drug could be retrieved in the urine, vs 51 % at Cl<sub>Cr</sub> 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 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 5 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 HES 130/0.4(50 mL Voluven 10%) per kg body weight /day. In rats, bolus injection of 5 g HES 130/0.4 (50mL Voluven 10%) during pregnancy and lactation reduced body weight of offspring and induced developmental delays. However, embryo-foetotoxicity in rats and rabbits was only observed at maternal-toxic dose levels which are 2.8 times greater than the maximum human therapeutic dose. Signs of fluid overloading were seen in the dams.

In a fertility study in rats only at the highest, maternal toxic dose of 5 g HES 130/0.4 per kg body weight given as a bolus, a slight decrease in the number of corpora lutea and implantation sites and therefore consequently for the mean number of foetuses was observed. This dose is 2.8 times greater than the maximum human therapeutic dose.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

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:

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**

Polyolefine 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 Polyolefine (freeflex) bag prior to use.

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

## **7 MARKETING AUTHORISATION HOLDER**

Fresenius Kabi Limited  
Cestrian Court  
Eastgate Way  
Manor Park  
Runcorn  
Cheshire  
WA7 1NT  
UK

## **8 MARKETING AUTHORISATION NUMBER**

PA0566/037/001

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 16th May 2008

## **10 DATE OF REVISION OF THE TEXT**

May 2018