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

Voluven 10% Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1000 ml solution for infusion contain:

Poly(O-2-hydroxyethyl)starch (Ph.Eur.) - Molar substitution: 0.38 – 0.45 - Mean molecular weight: 130,000 Da (manufactured from waxy maize starch)	100 g
Sodium chloride	9 g

Electrolytes:

Na^+	154 mmol/l
Cl^-	154 mmol/l

Theoretical osmolarity:	308 mosm/l
Titratable acidity:	< 1.0 mmol NaOH/l
pH:	4.0 – 5.5

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

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 anaphylactoid/anaphylactic reaction can be detected as early as possible. If an anaphylactic/anaphylactoid reaction

occurs (see section 4.8) the infusion should be discontinued immediately and appropriate emergency medical treatment initiated.

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 18 ml/kg for Voluven 10 %.

Regarding the dosage it has to be considered that the intravascular volume effect is greater than the infused volume.

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.

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 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 (anaphylactoid/anaphylactic) 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.

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 interaction studies have been performed.

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 Voluven 10% 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 Voluven 10 % no clinical data on exposed pregnancies are available.
However, animal studies with Voluven 10 % do not indicate direct or indirect harmful effects with respect to reproductive toxicity at human therapeutic doses (see section 5.3).
Voluven 10 % should be used during 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 Voluven 10 % should be made taking into account the benefit of breast-feeding to the child and the benefit of Voluven 10 % therapy to the woman.

4.7 Effects on ability to drive and use machines

Voluven 10 % 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). All patients receiving starch infusions should therefore be closely monitored for such reactions, the infusion discontinued immediately and appropriate emergency medical treatment initiated if necessary.

Skin and subcutaneous tissue disorders

Common (dose dependent): Prolonged administration of high dosages of hydroxyethyl starch causes 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 hematocrit.

Renal and urinary disorders

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

Hepatobiliary disorders

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

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 the national reporting system (see below):

Ireland
HPRA Pharmacovigilance,
Earlsfort Terrace
IRL – Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
E-mail: 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: Blood substitutes and plasma protein fractions, ATC code: B05AA07
Voluven 10 % 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 (10 %) as well as the dosage and infusion rate. Hydroxyethyl starch (130/0.4) contained in Voluven 10 % is manufactured from waxy maize starch and has a substitution pattern (C_2/C_6 ratio) of approximately 8-12.

Hydroxyethyl starch (130/0.4) contained in Voluven 10 % is derived from waxy maize starch and has a substitution pattern (C_2/C_6 ratio) of approximately 9:1.
Voluven 10 % is hyperoncotic, i.e., the increase in intravascular plasma volume exceeds the volume of the solution infused. Infusion of 500 ml of Voluven 10 % in 30 minutes in volunteers results in a relative increase of the subjects' blood volume by 20 % and an increase of the subjects' plasma volume by 32 %. The hypervolemic volume effect is maintained for approximately 5 to 6 hours.
Isovolemic exchange of blood with Voluven 6 % 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 and the substitution pattern (C_2/C_6 ratio). When administered 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 10 % in the plasma is about 65,000 Da 1.5 hours 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 10 % is still 81 % of the maximum concentration. After 6 hours the plasma level has decreased to 16 %. Following a single dose of 500 ml hydroxyethyl starch plasma levels almost return to baseline after 24 hours.
Plasma clearance was 26.0 ml/min when 500 ml of Voluven 10% was administered, with an AUC of 28.8 mg/ml x h, which shows a non-linear pharmacokinetic. Plasma half-lives were t 1/2α = 1.54 h and t 1/2ß = 12.8 h when 500 ml were administered on a single occasion.
Using the same dose (500 ml) of a 6 % solution 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 active substance HES 130/0.4 could be retrieved in the urine, vs 51 % at Cl_{Cr} 15 to 30 ml/min.
No significant plasma accumulation occurred after a daily administration of 500 ml of a Voluven 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 HES 130/0.4 per day 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 10 % in dialysis.

5.3 Preclinical safety data

Subchronic toxicity:
The intravenous infusion of 90 ml/kg b.w**.** /day Voluven 10 % 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 Voluven 10 %, which is at least 5 times greater than maximum human therapeutic dose levels.

Reproductive toxicity:
Voluven 10 % 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 (50 mL Voluven 10%) per kg body weight/day 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 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

The mixing with other medicinal products should be avoided. If, in exceptional cases, a mixture with other medicinal products 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:
Polyethylene bottle (KabiPac**,** made from LDPE): 3 years.

b) Shelf life after first opening of the container:
From a microbiological point of view the product should be used immediately.
If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

Polyethylene bottle (KabiPac, made from LDPE): 1 x 500 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 is opened.
Do not use Voluven 10 % after expiry date. Any unused solution should be discarded.
Any unused product or waste material should be disposed of in accordance with local requirements.
Use only clear-particle-free solutions and undamaged containers.

Keep out of reach of children.

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Limited
Cestrian Court
Eastgate Way
Manor Park
Runcorn
Cheshire
WA7 INT
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 0566/020/005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th August 2010

Date of last renewal: 12th March 2015

10 DATE OF REVISION OF THE TEXT

June 2018