VOLUVEN®
6% Solution for Infusion

PACKAGE LEAFLET

Voluven
6% Solution for Infusion

Hydroxyethyl starch (HES 130/0.4) in isotonic sodium chloride solution

Qualitative and quantitative composition
1000 ml contain:

Active constituents:

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/l
Cl^-	154 mmol/l
Other constituents:	
Sodium hydroxide	
Hydrochloric acid	
Water for injection	
Theoretical osmolarity	308 mosml/l
pH	4.0 - 5.5
Titratable acidity	< 1.0 mmol NaOH/l

Solution for intravenous infusion

Description

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

Pharmacodynamic properties

Voluven 6% 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 Voluven 6% is derived from waxy maize starch and has a substitution pattern (C_2/C_6 ratio) of approximately 9:1.

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 hours.

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 anesthesia. The occurrence of hypotension was significantly lower for Voluven 6% compared to crystalloid control (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.

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 $t\ 1/2\beta = 12.1$ 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 Voluven 6% 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 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 Contraindications).

Therapeutical indications

Treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient.

Contra-indications

- Hypersensitivity to the active substances or to any of the other excipients
- 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 hypernatremia or severe hyperchloremia
- Severely impaired hepatic function
- Congestive heart failure
- Severe coagulopathy
- Organ transplant patients

Special warnings and precautions for use

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

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.

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.

Avoid use in patients with pre-existing renal dysfunction.

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

Continue to monitor renal function in hospitalized patients for at least 90 days as use of RRT has been reported up to 90 days after administration of HES products.

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.

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 at the first sign of clinically relevant coagulopathy.

Pregnancy and lactation

For Voluven 6% no clinical data on exposed pregnancies are currently available.

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 anesthesia. No negative influence of Voluven 6% on patient safety could be detected; a negative influence on the neonate could also not be detected.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or postnatal development. 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.

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 6% should be made taking into account the benefit of breast-feeding to the child and the benefit of Voluven 6% therapy to the woman.

There are currently no clinical data available on the use of Voluven 6% in lactating women.

Interactions with other medicinal products and other forms of interaction

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

Please refer to section “Undesirable effects“ concerning the concentration of serum amylase which can rise during administration of hydroxyethyl starch and can interfere with the diagnosis of pancreatitis.

Posology and method of administration

For intravenous use as infusion.

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.

Voluven 6% can be administered repetitively over several days according to patient's needs. The dosage and duration of treatment depends on the duration and extent of hypovolaemia, the haemodynamics and on the haemodilution.

Adult dose:
Up to 50mL of Voluven per kg of body weight per day (equivalent to 3g hydroxyethyl starch and 7.7 mEq sodium per kg body weight). This is equivalent to 3500mL Voluven 6% for a 70kg patient.

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:
The dosage in children should be adapted to the individual patient colloids needs, taking into account the disease state as well as the hemodynamic and hydration status.

In 41 newborns to infant (< 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.

Overdose (symptoms, emergency procedure, antidotes)

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.

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), 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 rarely 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 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.

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.

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

Healthcare professionals should report any suspected adverse reaction of this medicinal product to the National Adverse Drug Reaction Monitoring Centre through online at www.bpfk.gov.my.

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.

Shelf life

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

Freeflex bag:	3 years
Polyethylene bottle (KabiPac):	5 years

b) Shelf life after first opening of the container:
The product should be used immediately after opening

Do not freeze. Do not store above 30 °C.

Special precautions for disposal and other handling

For single use only

To be used immediately after the bottle or bag is opened.

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

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

Remove the overwrap from the Polyolefine (freeflex) and PVC bag prior to use. Keep this medicine out of the sight and reach of children.

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

Date of revision

March 2017

Package sizes

Polyolefine bag (Freeflex) 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

Polyethylene bottle (bottelpack)
10 x 250 ml, 20 x 250 ml, 30 x 250 ml
10 x 500 ml, 20 x 500 ml
5000 ml

Not all pack sizes may be marketed

Manufacturer:
Fresenius Kabi Deutschland GmbH
D-61346 Bad Homburg v.d.H.
Tel.: +49 6172 6860

Imported by / Marketing Authorization Holder in Malaysia:
Fresenius Kabi Malaysia Sdn Bhd
3-1 & 3-2, Axis Technology Centre
Lot 13, Jalan 51A/225
46100 Petaling Jaya
Selangor, Malaysia
Tel.: +603-7957 2929

Fresenius Kabi Deutschland GmbH
D-61346 Bad Homburg v.d.H.

FRESENIUS
KABI