VOLUVEN®

6% HydroxyEthylStarch 130/0.4

PRODUCT MONOGRAPH

VOLUVEN® (6%) hydroxyethyl starch 130/0.4 in 0.9% sodium chloride Injection

Plasma Volume Expander

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non medicinal Ingredients
Intravenous	Solution for infusion	Poly (O-2-hydroxyethyl) starch (Molar substitution: 0.4) (Mean molecular weight: 130,000 Da) Sodium chloride pH adjusted with Sodium hydroxide or hydrochloric acid

For complete information see Dosage Forms, Composition and Packaging.

INDICATIONS AND CLINICAL USE

VOLUVEN® (6% HES 130/0.4) is indicated for the treatment of hypovolemia when plasma volume expansion is required.

It is not a substitute for red blood cells or coagulation factors in plasma.

CONTRAINDICATIONS

VOLUVEN® is contraindicated in patients with fluid overload (hyperhydration) and especially in cases of pulmonary edema and congestive cardiac failure.

VOLUVEN® should not be used in renal failure with oliguria or anuria not related to hypovolemia.

VOLUVEN® should not be administered in patients receiving dialysis treatment.

Solutions containing VOLUVEN® should not be administered to patients with severe hypernatremia or severe hyperchloremia.

VOLUVEN® is contraindicated in patients with known hypersensitivity to hydroxyethyl starch.

VOLUVEN® is contraindicated in patients with intracranial bleeding.

WARNINGS AND PRECAUTIONS

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 case of severe dehydration a crystalloid should be given first.

Caution should be observed before administering VOLUVEN® to patients with severe liver disease or severe bleeding disorders (e.g. severe cases of von Willebrand´s disease).

Administration of large volumes of hydroxyethyl starch may transiently alter the coagulation mechanism and decrease hematocrit and plasma proteins due to hemodilution.

Elevated serum amylase levels may be observed temporarily following administration of VOLUVEN® and can interfere with the diagnosis of pancreatitis.

It is important to supply sufficient fluid and to regularly monitor kidney function and fluid balance.

Serum electrolytes should be monitored.

Regarding the occurrence of anaphylactoid reactions please refer to section Adverse Reactions.

CARCINOGENESIS AND MUTAGENESIS:

No mutagenic effects were observed with HES 130/0.4 10% solution according to the following tests on mutagenic activity: Salmonella typhimurium reverse mutation assay (in vitro), mammalian cells in the in vitro gene mutation assay (HPRT), assessment of the clastogenic activity in cultured human peripheral lymphocytes (in vitro), bone marrow cytogenetic test in Sprague-Dawley rats.

PREGNANT WOMEN:

There are no adequate and well-controlled studies using VOLUVEN® in pregnant women. Reproduction studies performed in rats and rabbits have revealed no evidence of harm to the fetus due to VOLUVEN®. Embryotoxic effects were observed in rabbits at 50 mL/kg BW/day.

VOLUVEN® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING WOMEN:

It is not known whether HES 130/0.4 is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VOLUVEN® is administered to a nursing mother.

PEDIATRICS:

There is limited experience on the use of VOLUVEN® in children. In non-cardiac surgery of children below 2 years of age, the tolerability of VOLUVEN® administered perioperatively was comparable to 5% albumin. VOLUVEN® may be given to premature infants and newborns only after careful risk/benefit evaluation.

GERIATRICS:

Of the total number of patients in clinical trials of VOLUVEN® (N = 390), 26% were 65 years old or older. Other reported experience has not identified specific risks for the application of VOLUVEN® in this patient group.

ADVERSE REACTIONS

Adverse reactions with VOLUVEN® reported spontaneously, from clinical trials and in the literature include:

Anaphylactoid reactions (mild influenza-like symptoms, bradycardia, tachycardia, bronchospasm, non-cardiac pulmonary edema)

have been reported rarely 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.

The concentration of serum amylase can rise commonly during administration of hydroxyethyl starch and can interfere with the diagnosis of pancreatitis.

Pruritus (itching) is a known complication of administration of hydroxyethyl starches, though is typically more common with prolonged use of high doses. In the pivotal study, with patients monitored to 28 days post-operatively, pruritus occurred in 10.2% of cases in the VOLUVEN® group and 9.8% of cases in the hetastarch group. In both groups, pruritus was mild and self-limiting. However, HES-induced pruritus may be delayed in onset, typically one to six weeks after exposure, may be severe and may be of protracted (weeks and months) persistence. It is generally unresponsive to therapy. The decreased molecular weight, lower degree of substitution, decreased tissue storage and intra-vascular persistence in conjunction with a shorter plasma half-life of VOLUVEN® may result in a lower incidence of pruritus related to its use.

At high dosages the dilution effects may commonly result in a corresponding dilution of blood components such as coagulation factors and other plasma proteins and in a decrease of hematocrit.

With the administration of hydroxyethyl starches disturbances of blood coagulation can occur rarely depending on the dosage.

Table: Frequency of Occurrence of Adverse Drug Reactions

System Organ Class	Adverse Drug Reaction	Frequency of Occurrence
Blood and lymphatic system disorders	Coagulation disorders	Rare (in high doses) (> 0.01% - ≤ 0.1%)
Immune system disorders	Anaphylactoid reactions	Rare (> 0.01% - ≤ 0.1%)
Skin and subcutaneous tissue disorders	Pruritus	Common (dose dependent) (≥ 1% - < 10%)
Investigations	Increase of serum amylase	Common (dose dependent) (≥ 1% - < 10%)
	Decrease of hematocrit	Common (dose dependent) (≥ 1% - < 10%)
	Decrease of plasma proteins	Common (dose dependent) (≥ 1% - < 10%)

DRUG INTERACTIONS

Based on limited studies interactions are not known, however, mixing with other drugs should be avoided.

DOSAGE AND ADMINISTRATION

VOLUVEN® (6% HES 130/0.4) is **administered by intravenous infusion only.**
Total volume and rate of infusion are dependent on the clinical situation and the individual patient. As with any intravenous fluid, VOLUVEN® should be administered in accordance with accepted clinical practices for fluid and electrolyte management.

In clinical trials, infusions up to 33 mL/kg/day were most commonly used. There is limited experience with infusions up to 50 mL/kg/day.

The initial 10 - 20 mL are to be infused slowly, keeping the patient under close observation (due to possible anaphylactoid reactions).

VOLUVEN® can be administered repetitively over several days. The dosage and duration of treatment should be individualized according to the duration and extent of hypovolemia, the hemodynamic status and on the resultant hemodilution.

Children: Limited clinical data on the use of VOLUVEN® in children is available. In 41 children including newborns to infants (< 2 years), a mean dose of 16±9 mL/kg was administered safely and well tolerated for stabilization of hemodynamics.

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

OVERDOSAGE

As with all volume substitutes, overdose can lead to overloading of the circulatory system (e.g. pulmonary edema). In this case the infusion should be stopped immediately and if necessary, a diuretic should be administered.

ACTION AND CLINICAL PHARMACOLOGY

VOLUVEN®, 6% hydroxyethyl starch (HES 130/0.4), tetrastarch, is an artificial colloid, third generation starch, for volume replacement whose effect on intravascular volume expansion and hemodilution depends on the molar substitution by hydroxyethyl groups (0.4), the mean molecular weight (130,000 Da), the concentration (6%), the degree of substitution (C_2/C_6 ratio) of approx. 9:1 as well as the dosage and infusion rate.
Hydroxyethyl starch 130/0.4 is a derivative of thin boiling waxy maize starch, which mainly consists of a glucose polymer (amylopectin) predominately consisting of α-1.4-connected glucose units with several α-1.6-branches. The medium molecular weight (130,000 Da), low degree of substitution (0.4) and narrow molecular weight distribution of hydroxyethyl starch (HES 130/0.4) contained in VOLUVEN® contribute to its beneficial effects on pharmacokinetics, intravascular volume effect and hemodilution.

Pharmacodynamics
Infusion of 500 mL VOLUVEN® over 30 minutes in healthy 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. Isovolemic exchange of blood with VOLUVEN® maintains blood volume for at least 6 hours.

Pharmacokinetics

The pharmacokinetic profile of HES is complex and largely dependent on its molar substitution as well as its molecular weight. When administered intravenously, molecules smaller than the renal threshold (60,000 - 70,000 Da) are readily and rapidly excreted in the urine, while molecules with higher molecular weights are metabolised by plasma amylase prior to excretion via the renal route.

The mean *in vivo* molecular weight of VOLUVEN® in plasma is 70,000 - 80,000 Da immediately following infusion and remains above the renal threshold throughout the treatment period.

The volume of distribution of VOLUVEN® after intravenous administration of 500 mL to healthy volunteers is about 5.9 L. Plasma levels of VOLUVEN® remain at 75% of peak concentration at 30 minutes post-infusion and decrease rapidly to 14% at 6 hours post-infusion. Plasma levels of VOLUVEN® return to baseline levels 24 hours following infusion.

Plasma clearance of VOLUVEN® following intravenous administration of 500 mL was 31.4 mL/min with an AUC of 14.3 mg/mL/h, following non-linear pharmacokinetics. A single dose of 500 mL of VOLUVEN® results in elimination in the urine of approximately 62% within 72 hours. VOLUVEN® is eliminated from systemic circulation with a $t_{1/2}$ of 1.4 h and a terminal half life ($t_{1/2\beta}$) of 12.1 h following administration of a single dose of 500 mL.

The kinetics of VOLUVEN® are similar following single and multiple dose administration. No significant plasma accumulation occurred after daily administration of 500 mL of a 10% solution containing HES 130/0.4 over a period of 10 days. Elimination rates in the urine were approximately 70% within 72 hours.

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.

Special Populations and Conditions

Renal Insufficiency: Single intravenous administration of VOLUVEN® (500 mL) in subjects with mild to severe renal impairment resulted in a moderate increase in AUC by a factor of 1.7 (95% confidence limits 1.44 and 2.07) only in subjects with Cl_{Cr} < 50 mL/min compared to ≥ 50 mL/min. However, terminal half-life and peak HES concentration were not affected by renal impairment. Plasma levels of VOLUVEN® return to baseline levels 24 hours following infusion.

59% of HES 130/0.4 was recovered in the urine of subjects with Cl_{Cr} ≥ 30 mL/min versus 51% in those with Cl_{Cr} between 15 to 30 mL/min.

There is no data available on the use of VOLUVEN® in dialysis.

Hepatic Insufficiency: Pharmacokinetic data of patients with hepatic insufficiency are not available.

Age: Pharmacokinetic data of elderly or children are not available.

STORAGE AND STABILITY

To be used immediately after the bag is opened.

The solution is intended for intravenous administration using sterile equipment.

Use only clear solutions and undamaged containers.

Parenteral drug products should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used. Discard unused portion.

Do not use VOLUVEN® after expiry date.
free*flex*® bag storage at 15° - 25°C
The product should be used immediately after opening.
Do not freeze.

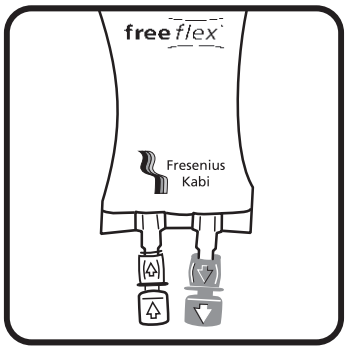
SPECIAL HANDLING INSTRUCTIONS

Before administering the product in plastic bags to patient, review these directions:

free*flex*® **IV Solution Container**

These instructions are only intended as guidelines for product use. Please refer to your own departmental guidelines.

1

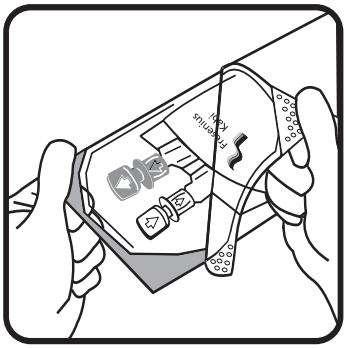


Preparation for administration

2

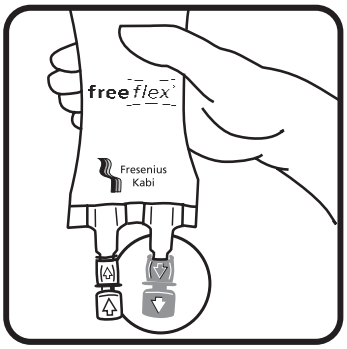
- Check the **free***flex*® IV container solution composition, lot number and expiry date.
- Inspect the container for damage or solution leakage. If damaged, do not use!
- Check the **free***flex*® solution for visible particles or cloudiness. Do not use unless the solution is clear.

3



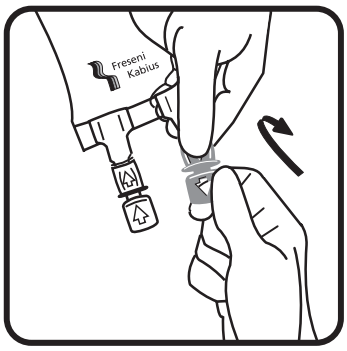
- Turn the **free***flex*® IV container over so that the text is face down. Using the pre-cut corner tabs peel open the overwrap to remove the primary bag. The overwrap adheres slightly to the primary bag to improve handling even when wearing disposable gloves.

4



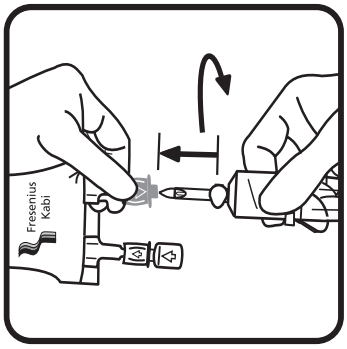
- Identify the blue infusion port. Check the **free***flex*® IV container solution for visible particles or cloudiness. Do not administer unless the solution is clear.

5



- Flip off the blue tamper-evident cover from the **free***flex*® IV container infusion port.

6



- Use a non-vented giving set or, if using a vented set, close the air inlet. Grip the base of the infusion port with your fingers behind the guard. Push and twist the giving set firmly into the port. A slight resistance should be felt, as the port membrane is broken. To prevent leaks, insert the spike until the clear plastic collar of the port meets the shoulder of the spike.

WARNINGS

1. Do not remove the **free***flex*® IV container from its overwrap until immediately before use.
2. Do not administer unless the solution is clear, free from particles and the **free***flex*® IV container is undamaged.
3. Discontinue the infusion if adverse reaction occurs.
4. Do not vent.
5. It is recommended that administration sets are changed at least once every 24 hours.
6. Partially-used **free***flex*® IV container must be discarded.

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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

VOLUVEN® (HES 130/0.4) is supplied sterile and pyrogen-free in 250 and 500 mL plastic bags (**free***flex*®) for intravenous infusion. The composition of each 100 mL is as follows:

Poly (O-2-hydroxyethyl) starch	6.00 g
(Molar substitution: 0.4)	
(Mean molecular weight: 130,000 Da)	
Sodium chloride	0.90 g
Water for injection	qs
pH adjusted with Sodium hydroxide or hydrochloric acid	qs

Approximate concentration of electrolytes per litre:

Sodium (Na^+) 154 mmol, Chloride (Cl^-) 154 mmol

Theoretical osmolarity	308 mosmol/litre
pH	4.0 - 5.5
Titratable acidity	< 1.0 mmol NaOH/litre

VOLUVEN® (HES 130/0.4) solution for infusion is supplied in the following primary containers of the following package sizes:
Polyolefine bag (**free***flex*®) with overwrap:
30 x 250 mL; 20 x 500 mL

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

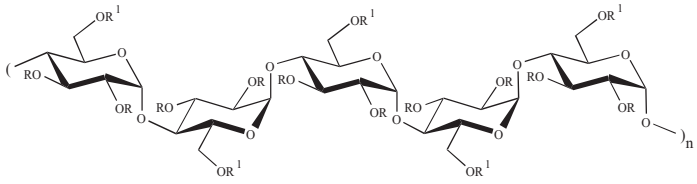
Description of Drug Substance

Hydroxyethyl starch is a derivative of amylopectin, which is a highly branched compound of starch. In humans and animals amylopectin is rapidly hydrolyzed by amylase. In order to reduce the metabolic degradation, glucose residues of the amylopectin are reacted with ethylene oxide. The hydroxyethyl groups can be introduced at three positions (C_2,C_3,C_6) of the glucose residues. The degree of substitution and the substitution pattern, expressed by the C_2/C_6 ratio, determine the enzymatic degradation of HES. VOLUVEN® (HES 130/0.4) is characterized by its molar substitution, by its molecular weight and the C_2/C_6 ratio.

Proper or common name: Hydroxyethyl Starch (HES) (130/0.4)

Chemical name: Poly (O-2 hydroxyethyl) starch

Structural formula:



R = -H, -CH_2CH_2OH
R^1 = -H, -CH_2CH_2OH or glucose units

Average Molecular weight: 110,000 - 150,000 Da

Molecular weight (Mw): The molecular weight indicates the weight average. The Mw of HES 130/0.4 lies between 110,000 and 150,000 Dalton, which corresponds approximately to 609 to 830 partially hydroxyethylated glucose units.

Molar substitution (MS): The ratio of hydroxyethyl groups to glucose units is called the molar substitution (MS). The molar substitution (MS) for this substance is 0.4 (0.38 - 0.45), tetrastarch, and determines the molar ratio of hydroxyethyl ether groups to glucose units.

C_2/C_6 ratio: This parameter gives information about the preferred position of hydroxyethylation and reflects the different intrinsic reactivity of the secondary and the primary alcohol functionality at the respective positions of the glucose ring. The value of the C_2/C_6 ratio should be higher than 8 for HES 130/0.4.

Product Characteristics: Hydroxyethyl starch (HES 130/0.4) 6% in isotonic sodium chloride solution is colorless and clear.

CLINICAL TRIALS

A prospective, controlled, randomised, double-blind, multi-center trial of 100 patients was conducted that evaluated VOLUVEN® (6% hydroxyethyl starch 130/0.4), compared to US approved 6% hetastarch 450/0.7 containing 0.9% saline, for intraoperative volume substitution during major orthopedic surgery. The primary efficacy parameter was the total volume of colloidal solution required.

The primary efficacy variable total volume of colloid solution required for intraoperative volume substitution was equivalent for the two treatment groups. Mean volume was 1613±778 mL for VOLUVEN® and 1584±958.4 mL for hetastarch. The ratio VOLUVEN®/hetastarch was estimated as 1.024 with a 95% confidence interval [0.84;1.25].

The results for the four primary safety variables are shown in the following table:

Variable	Mean		Ratio VOLUVEN®/Hetastarch	
	VOLUVEN® N = 49	Hetastarch N = 51	Estimate	95% CI
Calculated red blood cell loss [L]	1.17	1.31	0.910	[0.720;1.141]
Factor VIII [%]	100.5	81.4	1.244	[1.000;1.563]
von Willebrand factor [%]	97.7	88.7	1.128	[0.991;1.285]
Fresh frozen plasma (mL)	72	144	0.723	[0.000;2.437]

A significant difference between treatment groups in fluid input was found for the sum of erythrocyte volumes from packed RBC + salvaged blood + other blood in mL/kg body weight (8.0 mL/kg vs 13.8 mL/kg).

There were no significant differences noted between the two groups in serious adverse events. Three cases of serious coagulopathies occurred in the hetastarch group only. However, all three cases had also received high doses (> 3000 mL) which are known to increase the risk for effects of the drug on the coagulation system.

With respect to the secondary efficacy endpoints of hemodynamic stability, body temperature, hemodynamic parameters, BP, central venous pressure, heart rate, fibrinogen and platelets there was no statistically significant difference between the two treatment groups.

DETAILED PHARMACOLOGY

The pharmacodynamic effect of HES 130/0.4 6% was examined in a shock model in conscious rats and an exchange model in dogs. In both studies the control group received HES 200/0.5 6% (pentastarch).

HES 130/0.4 6% solution was as effective as HES 200/0.5 6% solution in maintaining cardio-pulmonary functions during isovolemic hemodilution in Beagle dogs. In the 3-hour follow-up period no additional administration of colloid was necessary.

There were no differences in long-term survival of rats after a single administration of HES 130/0.4 6% and HES 200/0.5 6% solution following an induced hemorrhagic shock (67% and 50% blood loss). In the HES 130/0.4 6% group bled at 67%, the survival rate was 83% since one animal died. However, non-survival of one animal lies within the normal range for this type of experiment. In the corresponding HES 200/0.5 6% group survival was 100%. Infusion of Ringer's lactate resulted in a 50% survival rate after a 50% blood loss and a 0% survival after a 67% blood loss. In conclusion, HES 130/0.4 6% had a life saving effect equivalent to HES 200/0.5 6% in this rat model.

After multiple I.V. administration of 0.7 g per kg BW per day of HES 130/0.4 10% or HES 200/0.5 10% solution during 18 consecutive days, the plasma HES concentration in rats treated with HES 130/0.4 10% was lower compared to rats treated with HES 200/0.5 10%. HES 130/0.4 10% was eliminated faster than HES 200/0.5 10%. In both groups, clear signs of HES tissue storage were detected in lymph nodes and spleen. Numerous empty vacuoles in macrophages were observed. Only a minimal cellular vacuolization was found in the liver and kidney. Histochemical differences between the groups were not observed.

Therefore, a study with radiolabelled ^{14}C-HES 130/0.4 10% and ^{14}C-HES 200/0.5 10% solutions was carried out. In animals treated with HES 130 radioactivity decreased from 4.3% of the total administered dose (2.6 g HES 130/animal) on day 3 to 0.6% on day 52. In animals treated with HES 200/0.5 the ^{14}C-activity decreased from 7.7% of the total administered dose (2.7 g HES 200/animal) on day 3 to 2.45% on day 52. These results confirm the faster elimination and lower persistence of HES 130/0.4 in tissue.

MICROBIOLOGY

Not applicable.

TOXICOLOGY

MUTAGENICITY STUDY

No mutagenic effects were observed with HES 130/0.4 10% solution according to the following tests on mutagenic activity: Salmonella typhimurium reverse mutation assay (in vitro), mammalian cells in the in vitro gene mutation assay (HPRT), assessment of the clastogenic activity in cultured human peripheral lymphocytes (in vitro), bone marrow cytogenetic test in Sprague-Dawley rats.

SENSITIZATION STUDY

In a skin sensitization study, 30 male Dunkin-Hartley guinea pigs were treated intracutaneously and topically with undiluted HES 130/0.4 10% to examine the local irritation. Animals of the control group were treated with isotonic NaCl solution (negative control). The positive control group was treated with potassium dichromate.

No skin irritation after application of HES 130/0.4 10% solution was observed. HES 130/0.4 10% has no sensitizing properties.

NON-ANTIGENICITY STUDY

A study in 5 female Dunkin-Hartley guinea pigs was done to demonstrate non-antigenicity of HES 130/0.4 10% in sensitized guinea pigs. After the 48-day sensitization period the animals received 3 mL of HES 130/0.4 10% intravenously.

No sensitizing properties of HES 130/0.4 10% were observed in this animal model (data on file).

TOXICOLOGY

Type	Species	Route	Test Article	No. & Sex	Dose	Dose / Duration	Parameters Evaluated	Significant Observations and Conclusions
Dose-range-finding (pilot study)	Sprague-Dawley rats	i.v.	HES 130/0.4 10% solution	10F, 10M	20, 40, 60, or 90 mL HES 130/0.4 10% solution per kg BW	Infused over 3 hours daily for 14 consecutive days	Local or systemic intolerance reactions	Dose-levels up to 90 mL/kg BW did not cause any substance-related local or systemic intolerance reactions
Dose-range finding (pilot study)	Beagle dogs	i.v	HES 130/0.4 10%	4F, 4M	20, 40, 60, or 90 mL/kg/day over 3 hours	14 consecutive days	Dose range that cause substance-related local and systemic intolerance reactions	Dogs treated with 90 mL/kg BW showed a reduction of daily food consumption by approximately 16% to 32% after one week of treatment. In one dog, increased salivation of 5 to 20 minutes duration was observed after the start of the 3rd and 5th infusion. Based on results, 60 and 90mL per kg BW were chosen for 13-week Tox study.
Subchronic	Sprague-Dawley rats	i.v.	HES 130/0.4 10% saline control	40F, 40M	60 mL HES 130/0.4 10% per kg BW 90 mL HES 130/0.4 10% per kg per BW 90 mL saline per kg BW	Infused over 3 hours daily for 91 consecutive days (13 weeks)	Clinical observations, clinical pathology, hematology, histopathology	No signs of toxicity, except for toxicity associated with increased workload related to the high doses forcing the animals to be under an unphysiological state for prolonged period. Rather than a direct toxic effect of the test compound the hematological, biochemical and histological findings observed were all considered to have resulted from the administration of large doses of HES with its oncotic property resulting in changes reflected by an increased work load on kidney and liver and the clear signs of uptake and storage of HES by the cells of the reticulo-endothelial system and in the hepatic parenchyma, renal tubular epithelium, transitional epithelium of the urinary bladder and mammary duct epithelium. No sex-related difference in toxicity.
Subchronic	Beagle dogs	i.v.	HES 130/0.4 10% saline control	3F, 3M 4F, 4M 4F, 4M	60 mL of HES 130/0.4 10% per kg BW 90 mL HES 130/0.4 10% per kg per BW 90 mL saline per kg BW	Infused over 3 hours daily for 91 consecutive days (13 weeks)	Clinical observations, clinical pathology, hematology, histopathology	No signs of toxicity, except for toxicity associated with increased work load related to high doses forcing the animals to be under an unphysiological state for a long period. Rather than a direct toxic effect of the test compound the haematological, biochemical and histological findings observed were all considered to have resulted from the administration of large doses of HES with its oncotic property resulting in changes reflected by an increased work load on kidney and liver and the clear signs of uptake and storage of HES by the cells of the reticulo-endothelial system and in the hepatic parenchyma, renal tubular epithelium, transitional epithelium of the urinary bladder and mammary duct epithelium. No sex-related difference in toxicity.

Type	Species	Route	Test Article	No. & Sex	Dose	Dose / Duration	Parameters Evaluated	Significant Observations and Conclusions
Teratology	Rats	i.v.	HES 130/0.4 10% isotonic NaCl solution	96F	12.5 mL of HES 130/0.4 10% per kg BW 25 mL of HES 130/0.4 10% per kg BW 50 mL of HES 130/0.4 10% per kg BW 50 mL of isotonic NaCl solution per kg BW	From the 6th to 17th day of pregnancy	Teratogenic properties	No effects were observed in rats and fetuses up to 12.5 mL of HES 130/0.4 10% per kg BW per day. At 25 mL of HES 130/0.4 10% per kg BW per day a slightly decreased food consumption and dyspnoea were observed in rats. At 50 mL of HES 130/0.4 10% per kg BW food consumption was reduced and signs of toxicity (dyspnoea and reduced motility) were observed. Administration of 25 or 50 mL of HES 130/0.4 10% per kg BW resulted in a decrease of mean fetal BW and in an increase of fetal incidences of skeletal retardations. These fetotoxic effects occurred only at maternal toxicity. HES 130/0.4 10% possesses no teratogenic properties.
Teratology	Rabbits	i.v.	HES 130/0.4 10% isotonic NaCl solution	48F	12.5 mL of HES 130/0.4 10% per kg BW 25 mL of HES 130/0.4 10% per kg BW 50 mL of HES 130/0.4 10% per kg BW 50 mL of isotonic NaCl solution per kg BW	From the 6th to 20th day of pregnancy	Teratogenic properties	No effects were observed in rabbits and fetuses up to 12.5 mL of HES 130/0.4 10% per kg BW per day. After administration of higher dose levels fetotoxic effects occurred only at maternal toxicity. HES 130/0.4 10% possesses no teratogenic properties.
Teratology Segment III	Rats	i.v	HES 130/0.4 10% isotonic NaCl solution	96F	12.5, 25, or 50 mL of HES 130/0.4 10% per kg BW	F_o generation from implantation through weaning: 6th day of gestation to 21st day of lactation	Development of the conceptus and offspring F_1 and F_2 generations: (Live birth index and overall survival index)	No adverse effects observed in F_o-dams, F_1 & F_2 generations with 12.5 mL/kg BW: HES 130/0.4 at 25 mL/kg BW: marginal decrease in food consumption for F_o dams. 50 mL/kg BW: F_o dams had an increased respiratory rate and decreased food consumption and BW. 5 dames died prematurely at end of gestation period and 2 died during littering. Results related to unphysiological hypervolemic state caused by bolus injection of drug and limitations of method of administration in this species. Total # of pups alive was within normal limits. The # of stillbirths was significantly higher compared to control. Reproduction parameters were slightly decreased, mean BW of pups (F_1) at birth significantly decreased and timepoints of ear opening, eye opening, vaginal opening delayed. Observed effect on BW subsided with time. All reproduction parameters in Pups of F_1 were similar to control group. None of pups from any of the doses were malformed. Therefore, HES 130/04 is non-materno-toxic and does not adversely affect F_1 and F_2 generations.

BLOOD COMPATIBILITY STUDY

A study to examine the hemolytic properties of HES 130/0.4 10% solution on human red blood cells was performed. Undiluted HES 130/0.4 10% solution was shown to have no hemolytic effect on human red blood cells.

LOCAL TOLERANCE

In a local tolerance study rabbits were administered a single intravenous infusion (300 mL HES 130/0.4 10% / 3 hours / animal), intra-arterially (300 mL HES 130/0.4 10% / 3 hours / animal), paravenously (0.5 mL HES 130/0.4 10% / animal), and subcutaneously (1 mL HES 130/0.4 10% / animal). 12 Himalayan rabbits (6 males and 6 females) were included into the study. Isotonic saline (NaCl 0.9%) served as a negative control.

Under these test conditions HES 130/0.4 10% showed good local tolerance in rabbits after intravenous infusion at a dose level that corresponded to 4 - 5 fold the level used in man. Microscopic investigations did not show any substance-related local changes.

Following further administration made erroneously (via intra-arterial, paravenous and subcutaneous infusion), HES 130/0.4 10% showed good tolerance comparable to the control solution.

REFERENCES

1. Waitzinger J, Bepperling F, Pabst G, et al. Hydroxyethyl starch (HES) [130/04], a new HES specification. Pharmacokinetics and safety after multiple infusions of 10% solution in healthy volunteers. Drugs R&D 2003; 4 (3): 149-57
2. Boldt J, Lehmann A, Römpert R, et al. Volume therapy with a new hydroxyethyl starch solution in cardiac surgical patients before cardiopulmonary bypass. J Cardiothor Vasc Anesth 2000; 14: 264-8
3. Bork K. Pruritus precipitated by hydroxyethyl starch: a review. Brit J Dermatol 2005, Jan;152(1):3-12
4. Boldt J, Haisch G, Suttner S, et al. Effects of a new modified, balanced hydroxyethyl starch preparation (Hextend®) on measures of coagulation. Br J Anaesth 2002; 89: 722-8
5. Boldt J, Brenner T, Lehmann A, et al. Influence of two different volume replacement regimens on renal function in elderly patients undergoing cardiac surgery: comparison of a new starch preparation with gelatin. Intensive Care Med 2003; 29: 763-9
6. Ellger B, Freyhoff J, van Aken H et al. High dose volume replacement using HES 130/0.4 during major surgery does not alter coagulation [abstract]. Eur J Anaesthesiol 2002; 19 (Suppl 24)
7. Gandhi S, Warltier D, Weiskopf R, Bepperling F, Baus D, Jungheinrich C. Volume substitution therapy with HES 130/0.4 (VOLUVEN®) versus HES 450/0.7 (hetastarch) during major orthopedic surgery. Crit. Care 2005; 9 (Suppl 1):206
8. Haisch G, Boldt J, Krebs C, et al. The influence of intravascular volume therapy with a new hydroxyethyl starch preparation (6% HES 130/0.4) on coagulation in patients undergoing major abdominal surgery. Anesth Analg 2001; 92: 565-71
9. Haisch G, Boldt J, Krebs C, et al. Influence of a New Hydroxyethylstarch Preparation (HES 130/0.4) on Coagulation in Cardiac Surgical Patients. Journal of Cardiothoracic and Vascular Anesthesia 2001; 15: 316-21
10. Hoffmann JN, Vollmar B, Laschke M, et al. Hydroxyethyl Starch (130 kD), but Not Crystalloid Volume Support, Improves Microcirculation during Normotensive Endotoxemia. Anesthesiology 2002, 97: 460-70
11. Huet G, Siemons AW, Baus D, et al. A novel hydroxyethyl starch (VOLUVEN®) for effective perioperative plasma volume substitution in cardiac surgery. Can J Anaesth 2000; 47: 1207-15
12. Ickx BE, Rigolet M, Van der Linden PJ. Cardiovascular and metabolic response to acute normovolemic hemodilution. Anesthesiology 2000; 93: 1011 - 6
13. Jungheinrich C, Scharpf R, Wargenau M, et al. The pharmacokinetics and tolerability of an intravenous infusion of the new hydroxyethyl starch 130/0.4 (6%, 500mL) in mild-to-severe renal impairment. Anesth Analg 2002; 95: 544 - 51
14. Jungheinrich C, Sauermann W, Bepperling F, Vogt NH: Volume efficacy and reduced influence on measures of coagulation using hydroxyethyl starch 130/0.4 (6%) with an optimised *in Vivo* molecular weight in orthopaedic surgery - a randomised, double-blind study. Drugs R&D 2004; 5(1):1-9
15. Jungheinrich C, Neff T: Pharmacokinetics of Hydroxyethyl Starch. Clin Pharmacokinetik 2005;44 (7):681-699
16. Kasper SM, Strömich A, Kampe S, et al. Evaluation of a New hydroxyethyl starch solution (HES 130/0.4) in patients undergoing preoperative autologous blood donation. J Clin Anesth 2001; 13: 486-90

17. Kasper SM, Meinert P, Kampe S, et al. Large-dose Hydroxyethyl Starch 130/0.4 Does Not Increase Blood Loss and Transfusion Requirements in Coronary Artery Bypass Surgery Compared with Hydroxyethyl Starch 200/0.5 at Recommended Doses. Anesthesiology 2003; 99: 42-7

18. Koehler H, Kirch W, Weihrauch TR, et al. Macroamylasia after treatment with hydroxyethyl starch. Eur J Clin Invest 1977; 7: 205-11

19. Köhler H, Zschiederich H, Linfante A, Appel F, Pitz H, Clasen R; The elimination of Hydroxyethyl Starch 200/0.5 , Dextran 40 and Oxypolygelatin. Klin Wochenschr 60, (1982); 293 - 301

20. Kozek-Langenecker S: Effects of Hydroxyethyl Starch Solutions on Hemostasis. Anesthesiology 2005; 103: 654-60

21. Lang K, Boldt J, Suttner S, et al. Colloids versus crystalloids and tissue oxygen tension in patients undergoing major abdominal surgery. Anesth Analg 2001; 93: 405-9

22. Langeron O, Doelberg M, Eng-Than A, et al. Volume replacement during major orthopedic surgery: a new 6% hydroxyethyl starch solution (HES 130/0.4) might reduce blood loss. Anesth Analg 2001; 92: 855-62

23. Leuschner J, Opitz J, Winkler A, Scharpf R, Bepperling F. Tissue storage of ^{14}C-labelled hydroxyethyl starch (HES) 130/0.4 and HES 200/0.5 after repeated intravenous administration to rats. Drugs R&D 2003; 4 (6): 331-8

24. Lochbühler H, Galli C, Hagemann H, Hydroxyethyl starch HES 130/0.4 in paediatric surgery: results of an explorative, controlled, multicenter safety study. Crit Care 2003; 7: 107

25. Neff TA, Dölberg M, Jungheinrich C, et al. Repetitive large-dose, infusion of the novel hydroxyethyl starch HES 130/0.4 in patients with severe head injury. Anesth Analg 2003;96:1453-9

26. Rudolf J. Hydroxyethyl Starch for Hypervolemic Hemodilution in Patients with Acute Ischemic Stroke: A Randomized, Placebo-Controlled Phase II Safety Study, Cerebrovascular Diseases 2002; 14: 33-41

27. Standl T, Burmeister MC, Schroeder F, et al. Hydroxyethyl starch (HES) 130/0.4 provides larger and faster increases in tissue oxygenation in comparison with prehemodilution values of HES 70/0.5 or HES 200/0.5 in volunteers undergoing acute normovolemic hemodilution. Anesth Analg 2003; 96: 936 - 43

28. Van der Linden Ph, De Hert S et al.: Hydroxyethyl Starch 130/0.4 Versus Modified Fluid Gelatin for Volume Expansion in Cardiac Surgery Patients: The Effects on Perioperative Bleeding and Transfusion Needs. Anesth Analg 2005;101:629-34

29. Waitzinger J, Bepperling F, Pabst G, et al. Pharmacokinetics and tolerability of a new hydroxyethyl starch (HES) specification [HES (130/0.4)] after single-dose infusion of 6% or 10% solutions in healthy volunteers. Clin Drug Invest 1998; 16: 151-60

30. Waitzinger J, Bepperling, F, Pabst G, et al. Effect of a new hydroxyethyl starch (HES) specification [6% HES (130/0.4)] on blood and plasma volumes after bleeding in 12 healthy male volunteers. Clin Drug Invest 1999; 17: 119-25

PART III: CONSUMER INFORMATION

VOLUVEN® (6%) hydroxyethyl starch 130/0.4 in 0.9% sodium chloride Injection.

This leaflet is part III of a three-part "Product Monograph" published when VOLUVEN® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about VOLUVEN®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What VOLUVEN® is used for:
VOLUVEN® (6% HES 130/0.4) is indicated for the treatment of hypovolemia when plasma volume expansion is required.

It is not a substitute for red blood cells or coagulation factors in plasma.

What VOLUVEN® does:
VOLUVEN®, 6% hydroxyethyl starch 130/0.4 (HES 130/0.4), tetrastarch, is an artificial colloid third generation starch for volume replacement. HES 130/0.4 is a novel hydroxyethyl starch for the treatment of hypovolemia when plasma volume expansion is required.

When it should not be used:
Your doctor will not administer VOLUVEN® if:

- you have too much fluid in your body and you have been told that you have a condition known as hyperhydration
- you have been told that you have pulmonary edema where too much fluid is in your lungs
- you have been told that you have a congestive heart failure (a condition in which your heart cannot pump enough blood to other organs of your body)
- you have kidney failure and you produce little or no urine and if this is not caused by low blood volumes (hypovolemia)
- you are receiving dialysis treatment (an artificial kidney treatment)
- you suffer from bleeding within or around the brain (intracranial bleeding)
- you have severely elevated plasma levels of either sodium or chloride (severe hypernatremia or severe hyperchloremia)
- you are allergic (hypersensitive) to hydroxyethyl starch or any of the other ingredients.

The composition of each 100 mL is as follows:
What the medicinal ingredient is:

Poly (O-2-hydroxyethyl) starch	6.00 g
(Molar substitution: 0.4)	
(Mean molecular weight: 130,000 Da)	

What the important non-medicinal ingredients are:

Sodium chloride	0.90 g
pH adjusted with Sodium hydroxide or hydrochloric acid	qs
Water for injection	qs

Approximate concentration of electrolytes per litre:
Sodium (Na^+) 154 mmol, Chloride (Cl^-) 154 mmol

What dosage form it comes in:
Solution for Infusion
(6%) hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection.

WARNINGS AND PRECAUTIONS

a) Tell your doctor, before administration, if:

- You have heart or kidney problems
- You have severe liver disease or bleeding disorders

b) Other warnings and precautions:

- Your doctor will be careful not to exceed the recommended dose as this may cause fluid

overload which may change blood conditions such as the ability for the blood to clot (coagulation), or alter blood factors (hematocrit, blood proteins).
- Your doctor may monitor your kidney function, your blood serum electrolytes and fluid balance to maintain adequate hydration.
- This medicine may temporarily increase the level of the enzyme serum amylase and could interfere with the diagnosis of inflammation of the pancreas (pancreatitis) (see Side Effects and What to Do About Them)
- Allergic reactions to the formulation may occur (see Side Effects and What to Do About Them).

USE IN PREGNANCY

There are no adequate and well-controlled studies using VOLUVEN® in pregnant women. Reproduction studies performed in rats and rabbits have revealed no evidence of harm to the fetus due to VOLUVEN®. Embryotoxic effects were observed in rabbits at 50 mL/kg BW/day. VOLUVEN® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING WOMEN

It is not known whether HES 130/0.4 is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VOLUVEN® is administered to a nursing mother.

PEDIATRICS

There is limited experience on the use of VOLUVEN® in children.

GERIATRICS

VOLUVEN® can be used in this patient group.

INTERACTIONS WITH THIS MEDICATION

Based on limited studies interactions are not known, however, mixing with other drugs should be avoided.

PROPER USE OF THIS MEDICATION

VOLUVEN® is administered by intravenous infusion only. The dosage and duration of treatment should be individualized and the physician will determine the appropriate dosing.

Children: Limited clinical data on the use of VOLUVEN® in children is available.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side Effects reported for this medicine include:

Rare (occurring in between one in a thousand and one in ten thousand patients)
- Allergic reactions with symptoms such as mild flu-like symptoms; ie fever, headache, slow heartbeat (bradycardia), fast heartbeat (tachycardia), bronchitis, fluid in the lungs unrelated to heart problems.
- Disturbances in blood clotting can occur, especially at higher doses. If this occurs the infusion will be stopped and treatment given as appropriate.

Common (occurring in between one in ten and one in a hundred patients)
- Itching is a known complication of administration of hydroxyethyl starches, though is typically more common with prolonged use of high doses.
- Other effects are associated with the dilution of the blood and its components (ie platelets, red blood cells, proteins), which occurs at high dosages, such as prolonged blood

clotting time and which might necessitate replacement of blood products.

- The level of the enzyme serum amylase can rise during administration of hydroxyethyl starch and can interfere with the diagnosis of inflammation of the pancreas (pancreatitis); however, VOLUVEN® 6% does not cause pancreatitis.

If you suffer such effects, tell your doctor.

This is not a complete list of side effects. If you have any unexpected effects after receiving VOLUVEN®, contact your doctor or pharmacist.

HOW TO STORE IT

To be used immediately after the bag is opened.

Use only clear solutions and undamaged containers.

Parenteral drug products should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used. Discard unused portion.

Do not use VOLUVEN® after expiry date.

free*flex*® bag storage: at 15° - 25° C

The product should be used immediately after opening.

Do not freeze.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program, collects information on serious and unexpected side effects of drugs.
If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By: toll-free telephone: 866-234-2345
By: toll-free fax 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Canada Vigilance, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.fresenius-kabi.ca
or by contacting Fresenius Kabi Canada at:
1-877-953-9002 (toll-free telephone)

This leaflet was prepared by Fresenius Kabi Deutschland GmbH
D-61346 Bad Homburg v.d.H.
Germany

Fresenius Kabi

Distributed by:
Fresenius Kabi Canada
a division of Calea Ltd.
2785 Skymark Ave. Unit 2
Mississauga, ON
L4W 4Y3
Canada

Date of Revision: 03 October 2007

V003E
Print date: November 2007