

Dear Healthcare Professional,

Fresenius Kabi is pleased to announce the Canadian availability of our latest innovation in Plasma Volume Expansion: VOLUVEN® (6% HES 130/0.4). VOLUVEN® has been used internationally for more than 6 years with **more than 12,000,000 patient exposures in 82 countries**.¹

Since the early 1970s, Fresenius Kabi has had an ongoing investment in research and development in plasma volume expansion technology. The R&D program is focused on refining the physicochemical properties of our HES products.

With **carefully balanced physicochemical properties of molecular weight, degree of molar substitution and narrow molecular weight distribution (HES 130/0.4)**, VOLUVEN® is Fresenius Kabi's most technologically advanced offering in HES plasma volume expansion.

For more details regarding VOLUVEN®, please see the enclosed prescribing information.

VOLUVEN® (6% HES 130/0.4 in 0.9% sodium chloride injection) 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.

VOLUVEN® is contraindicated in: patients with fluid overload (hyperhydration) and especially in cases of pulmonary edema and congestive cardiac failure; patients with known hypersensitivity to hydroxyethyl starch; patients with intracranial bleeding. VOLUVEN® should not be used in renal failure with oliguria or anuria not related to hypovolemia, or in patients receiving dialysis treatment, or in patients with severe hypernatremia or severe hyperchloremia.

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.

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).

Common (≥1% - <10%) adverse events included pruritus, serum amylase increase and decreased hematocrit and plasma proteins.

For complete information, including dosing, patient selection, warnings and precautions, please see the enclosed prescribing information.

If you would like a Fresenius Kabi Hospital Product Specialist representative to provide a presentation or more information on VOLUVEN® **please call 1-877-953-9002**.

Sincerely,



Janice Martin, Brand Manager



VOLUVEN®

6% Hydroxyethyl Starch 130/0.4

(6%) hydroxyethyl starch 130/0.4 in 0.9% sodium chloride Injection
Plasma Volume Expander

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 cystogenetic 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 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 stabilisation 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), is an artificial colloid 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 \geq 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.

freeflex® bag storage: at 15° - 25° C

The product should be used immediately after opening

Do not freeze.

DOSAGE FORMS, COMPOSITION AND PACKAGING

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

Poly (O-2-hydroxyethyl starch) (Molar substitution 0.38 - 0.45) (Mean molecular weight: 130,000 Da)	6.00 g
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
Titrateable 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 (**freeflex®**) with overwrap: 30 x 250 mL; 20 x 500 mL

Full product monograph available by contacting Fresenius Kabi Canada at: 1-877-953-9002 (toll-free-telephone)



Distributed by:

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Printed September 2006

References:

1. VOLUVEN® Product Monograph, Fresenius Kabi, March 2006
2. Waitzinger J, *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 (2) 119-125.
3. Data on file, Fresenius Kabi.

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