PRODUCT MONOGRAPH

VOLULYTE®

6% hydroxyethyl starch 130/0.4 in an isotonic electrolyte injection

Plasma Volume Expander

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Intravenous	Solution for infusion / 6% HES 130/0.4 in an isotonic electrolyte injection	Magnesium chloride hexahydrate, Potassium chloride, Sodium acetate trihydrate, Sodium chloride, Water for injections pH adjusted with sodium hydroxide or

INDICATIONS AND CLINICAL USE

VOLULYTE® is indicated for the treatment of hypovolemia due to acute blood loss when crystalloids alone are not considered sufficient.

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

CONTRAINDICATIONS

VOLULYTE® is contraindicated in patients:

- with fluid overload (hyperhydration), especially in cases of pulmonary edema and congestive cardiac failure.
- with sepsis.
- with renal impairment with oliguria or anuria not related to hypovolemia.
- with critical illness (typically admitted to the intensive care unit).
- with severe liver disease.
- receiving dialysis treatment.
- with severe hyperkalemia, severe hypernatremia or severe hyperchloremia.

- with known hypersensitivity to hydroxyethyl starch.
- with intracranial bleeding.
- with pre-existing coagulation or bleeding disorders.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- In critically ill patients, including patients with sepsis, use of hydroxyethyl starch (HES) products, including VOLULYTE®, increase risk of mortality and renal replacement therapy.
- Do not use HES products, including VOLULYTE®, in critically ill patients, including patients with sepsis.

General:

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.

Fluid status and rate of infusion should be assessed regularly during treatment, especially in patients with cardiac insufficiency or severe kidney dysfunction.

In case of severe dehydration a crystalloid should be given first. Generally, sufficient fluid should be administered in order to avoid dehydration.

Particular care must be taken in patients with electrolyte abnormalities like hyperkalemia, hypernatremia, hypermagnesemia, and hyperchloremia. In metabolic alkalosis and clinical situations where alkalization should be avoided, saline based solutions like a similar product containing HES 130/0.4 in 0.9% sodium chloride solution should be preferred over alkalizing solutions like VOLULYTE®.

Clinical evaluation and periodic laboratory determinations are necessary to monitor fluid balance, serum electrolyte concentrations, kidney function, acid-base balance, and coagulation parameters during prolonged parenteral therapy or whenever the patient's condition warrants such evaluation.

Carcinogenesis and Mutagenesis:

See PART II: SCIENTIFIC INFORMATION – Toxicology – Mutagenicity study.

Hematologic:

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 VOLULYTE® at the first sign of clinically relevant coagulopathy.

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

Hepatic/Biliary/Pancreatic:

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.

Monitor liver function in patients receiving HES products, including VOLULYTE®.

Immune:

Anaphylactic/anaphylactoid reactions (hypersensitivity, mild influenza-like symptoms, bradycardia, tachycardia, bronchospasm, non-cardiac pulmonary edema) have been reported 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 (please refer to section ADVERSE REACTIONS).

Renal:

Avoid use in patients with pre-existing renal dysfunction.

Discontinue use of VOLULYTE® at the first sign of clinically relevant renal injury.

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

Skin:

Pruritus is a known complication of administration of hydroxyethyl starches, though is typically more common with prolonged use of high doses.

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.

Special populations

Pregnant Women:

No clinical data with VOLULYT® on exposed pregnancies is available. However, animal studies with a similar product containing HES 130/0.4 in 0.9% sodium chloride solution do not indicate harmful effects with respect to embryo/fetal development, pregnancy, parturition or postnatal development. There were no post-marketing reports of harm when HES 130/0.4 in 0.9% sodium chloride solution was used in pregnant women.

Embryotoxic effects were observed in rabbits when 10% HES 130/0.4 in 0.9 sodium chloride solution is given at 50 mL/kg BW/day. No evidence of teratogenicity was observed.

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

Information on the use of VOLULYTE® during labour or delivery is unknown. Use if clearly needed.

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 VOLULYTE® is administered to a nursing mother.

A decision on whether to continue/discontinue breast-feeding or to discontinue/continue therapy with VOLULYTE® should be made taking into account the benefit of breast-feeding to the child and the benefit of VOLULYTE® therapy to the nursing mother.

Pediatrics:

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

Geriatrics:

Of the total number of patients in clinical trials of a similar product containing 6% HES 130/0.4 in 0.9% sodium chloride solution (N=471), 25% were 65-75 years old, while 7% were 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported experience has not identified specific risks for the application of 6% HES 130/0.4 in this patient group.

ADVERSE REACTIONS

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

Immune system disorders

Rare: Anaphylactic/anaphylactoid reactions (hypersensitivity, mild influenza-like symptoms, bradycardia, tachycardia, bronchospasm, non-cardiac pulmonary edema) have been reported with solutions containing hydroxyethyl starch (see WARNINGS AND PRECAUTIONS).

Abnormal Hematologic and Clinical Chemistry Findings (Investigations)

Common (dose dependent): Increase in serum amylase (see WARNINGS AND PRECAUTIONS)**.**

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.

Skin and subcutaneous tissue disorders

Common (dose dependent): Pruritus**,** itching (see WARNINGS AND PRECAUTIONS).

Blood and lymphatic system disorders

Rare (in high dose): Blood coagulation disturbances beyond dilution effects can occur 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 beyond dilution effects	Rare (in high doses) (>0.01% – ≤ 0.1%)
Immune system disorders	Anaphylactic/ anaphylactoid reactions	Rare (>0.01% – ≤ 0.1%)
Skin and subcutaneous tissue disorders	Pruritus	Common (dose dependent) (≥1% – < 10%)
Abnormal hematologic and clinical chemistry findings (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

No interactions of VOLULYTE® with other drugs or nutritional products are known or have been reported to date.

VOLULYTE® must not be mixed with other medicinal products.

Consideration should be given to the concomitant administration of medicinal products that can cause potassium or sodium retention.

DOSAGE AND ADMINISTRATION

VOLULYTE® (6% HES 130/0.4 in an isotonic electrolyte injection) 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, VOLULYTE® 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 between 33

mL/kg/day and 50 mL/kg/day.

The initial 10-20 mL is to be infused slowly, keeping the patient under close observation for possible anaphylactic/anaphylactoid reactions.

VOLULYTE® can be administered repetitively over several days according to the patient's needs. The dosage and duration of treatment depends on the duration and extent of hypovolemia, the hemodynamics and on the hemodilution.

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

OVERDOSAGE

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

For further information on the management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

VOLULYTE® contains 6% hydroxyethyl starch (HES 130/0.4), a tetrastarch. HES 130/0.4 is an artificial colloid, third generation starch, for volume replacement which is characterized by the molar substitution by hydroxyethyl groups (0.4), the mean molecular weight (130 000 Da), the concentration (6%), and the substitution ratio (C2/C6 ratio) of approximately 9:1. The effect on intravascular volume expansion and hemodilution depends on these parameters as well as on 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 VOLULYTE® contribute to its beneficial effects on pharmacokinetics and intravascular volume effect.

Pharmacodynamics

Infusion of 500 mL of 6% HES 130/0.4 in 0.9% sodium chloride solution 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 6% HES 130/0.4 in 0.9% sodium chloride solution maintains blood volume for at least 6 hours.

The electrolyte content of VOLULYTE® has been adapted to the principal ionic constituents of normal plasma. VOLULYTE® contains the electrolytes sodium (Na+), potassium (K+), magnesium (Mg++), chloride (Cl-) and acetate (CH3COO-) in an isotonic composition. Acetate is a metabolizable anion which is oxidized in different organs and has an alkalizing effect.

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 6% HES 130/0.4 in plasma is 70 000 – 80000 Da immediately following infusion and remains above the renal threshold throughout the treatment period.

The volume of distribution of 6% HES 130/0.4 after intravenous administration of 500 mL to healthy volunteers is about 5.9 L. Plasma levels of 6% HES 130/0.4 remain at 75% of peak concentration at 30 minutes post-infusion and decrease rapidly to 14% at 6 hours post-infusion. Plasma levels of 6% HES 130/0.4 return to baseline levels 24 hours following infusion.

Plasma clearance of 6% HES 130/0.4 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 6% HES 130/0.4 solution results in elimination in the urine of approximately 62% within 72 hours. Six percent HES 130/0.4 is eliminated from systemic circulation with a $t_{1/2\alpha}$ of 1.4 h and a terminal half life ($t_{1/2ß}$) of 12.1 h following administration of a single dose of 500 mL.

The kinetics of 6% HES 130/0.4 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 7 mL/kg BW per day of 10% 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 6% HES 130/0.4 (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 6% HES 130/0.4 return to baseline levels 24 hours following infusion.

Fifty-nine percent 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 VOLULYTE® in dialysis.

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

Age: Pharmacokinetic data in 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 VOLULYTE® after expiry date.

free*flex*® bag storage: at 15 °C – 25 °C for 3 years.

Do not freeze.

SPECIAL HANDLING INSTRUCTIONS

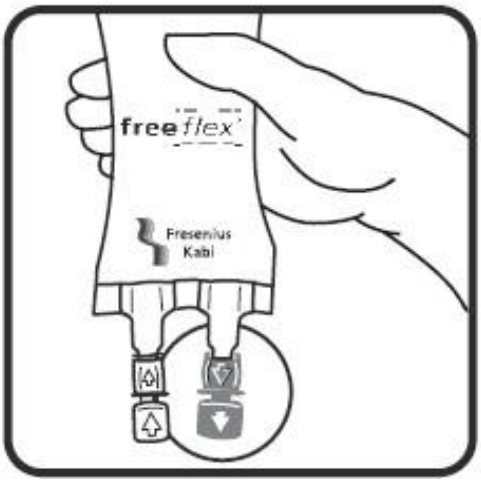
Before administering the product in plastic bags to patient, review these directions:

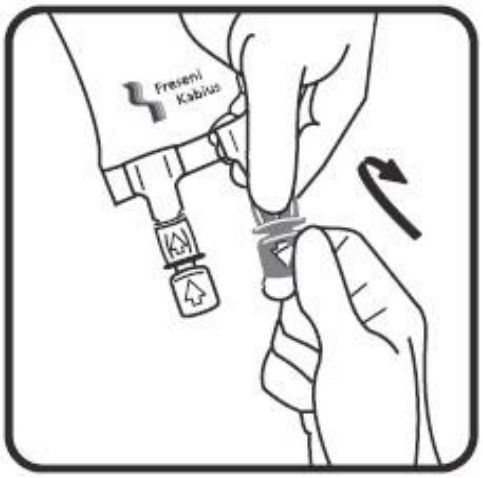
free*flex*® IV Solution Container

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

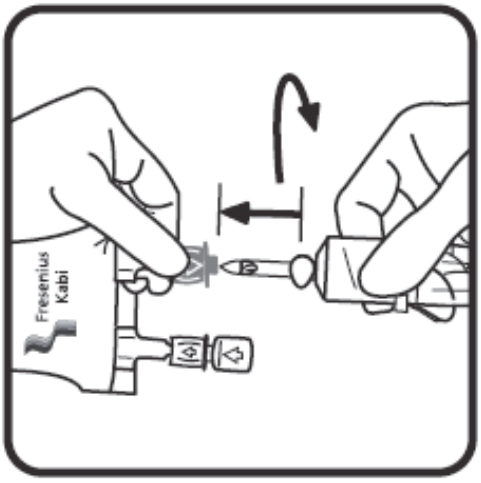
1. Check the solution composition, lot number and expiry date, inspect the container for damage or leakage, if damaged do not use.

2. Use opening aid to remove over-wrap





3. Identify the blue infusion (administration) port.



4. Break off the blue tamper-evident cover from the freeflex® infusion port.

5. Close roller clamp. Insert the spike until the clear plastic collar of the port meets the shoulder of the spike

6. Use a non-vented standard infusion set and close air inlet.

7. Hang the bag on the infusion stand. Press drip chamber to get fluid level. Prime infusion set. Connect and adjust the flow rate.

WARNINGS

1. Do not remove the **free***flex*® IV container from its overwrap until immediately before use.

2. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

3. Do not administer unless the solution is clear, free from particles and the **free***flex*® IV container is undamaged.

4. VOLULYTE® should be used immediately after insertion of the administration set.

5. Discontinue the infusion if adverse reaction occurs.

6. Do not vent.

7. It is recommended that administration sets are changed at least once every 24 hours.

8. For single use only. Discard unused portion.

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

VOLULYTE® (6% hydroxyethyl starch 130/0.4 in an isotonic electrolyte injection) 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 (Molar substitution: 0.4) (Mean molecular weight: 130 000 Da)	6.00 g
Sodium chloride	602 mg
Sodium acetate trihydrate	463 mg
Potassium chloride	30 mg
Magnesium chloride hexahydrate	30 mg
pH adjusted with sodium hydroxide or hydrochloric acid 25%	
Water for injection	q.s
Approximate concentration of electrolyte (mmol/L):	
Sodium (Na^+)	137.0
Potassium (K^+)	4.0
Magnesium (Mg^{++})	1.5
Chloride (Cl^-)	110.0
Acetate (CH_3COO^-)	34.0
Theoretical osmolarity (mosmol/L)	286.5
Titratable acidity (mmol NaOH/L)	< 2.5
pH	5.7 – 6.5

VOLULYTE®, 6% HES 130/0.4 in an isotonic electrolyte injection, is supplied in the following primary containers of the following package sizes:
Polyolefin bag (**free***flex*®) with overwrap: 10, 20, 30, 35, 40 x 250 mL; 10, 15, 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. HES 130/0.4 contained in VOLULYTE® is characterized by its molar substitution, molecular weight and the C_2/C_6 ratio.

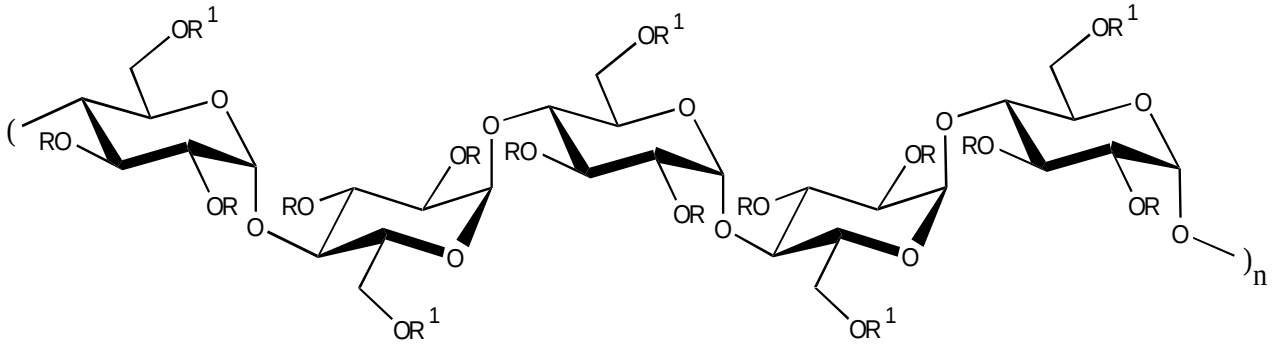
Proper or common name:

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 Dalton

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 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 (6% HES 130/0.4, a tetrastarch) in an isotonic electrolyte solution is a clear to slightly opalescent solution, colourless to slightly yellow.

CLINICAL TRIALS

A prospective, randomized, double-blinded, parallel group study in 81 patients undergoing cardiac surgery compared the efficacy and safety of two different 6% HES 130/0.4 formulations: VOLUVEN® and VOLULYTE®. The results showed that VOLULYTE® and VOLUVEN® were therapeutically equivalent regarding the volume of each product needed for adequate plasma volume expansion.

The safety of VOLULYTE® was not significantly different from the observed with VOLUVEN®. There was no evidence that the addition of Mg^{++}, K^{+}, and acetate in the solvent of VOLULYTE® in comparison to saline solutions influences coagulation parameters or bleeding events, as both the measured and calculated red blood cell loss showed no differences between treatment groups in this study.

Groups were comparable with regard to overall safety.

DETAILED PHARMACOLOGY

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

Six percent HES 130/0.4 solution was as effective as 6% HES 200/0.5 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 6% HES 130/0.4 and 6% HES 200/0.5 solution following an induced hemorrhagic shock (67% and 50% blood loss). In the 6% HES 130/0.4 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 6% HES 200/0.5 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, 6% HES 130/0.4 had a lifesaving effect equivalent to 6% HES 200/0.5 in this rat model. After multiple I.V. administration of 0.7 g per kg BW per day of 10% HES 130/0.4 or 10% HES 200/0.5 solution during 18 consecutive days, the plasma HES concentration in rats treated with 10% HES 130/0.4 was lower compared to rats treated with 10% HES 200/0.5. Ten percent HES 130/0.4 was eliminated faster than 10% HES 200/0.5. 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 radio-labelled 10% ^{14}C-HES 130/0.4 and 10% ^{14}C-HES 200/0.5 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

Repeated-Dose Toxicity

The intravenous infusion of 90 mL of 10% HES 130/0.4 per kg BW/day infused over 3 hours each day in rats and dogs for 3 months resulted in no signs of overt toxicity, except for an 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.

Reproductive Toxicity

HES 130/0.4 had no teratogenic properties in rats or rabbits. Embryolethal effects were observed in rabbits at 50 mL/kg BW/day of 10% HES 130/0.4. In rats, bolus injection of this dose during pregnancy and lactation reduced body weight of offspring and induced developmental delays. However, embryo-feto-toxicity in rats and rabbits was only observed at maternal-toxic dose levels. Signs of fluid overloading were seen in the dams. Fertility studies on directly exposed animals have not been conducted.

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.

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. an in vitro study, both VOLULYTE® and 6% HES 130/0.4 in

0.9% sodium chloride solution did not cause hemolysis in human whole blood.

Local tolerance

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

Under these test conditions 10% HES 130/0.4 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.

In a further local tolerance test in New Zealand White rabbits, both VOLULYTE® and 6% HES 130/0.4 in 0.9% sodium chloride solution were administered in intended intravenous administration site as well as in unintended injection sites (intraarterial, paravenous, subcutaneous and intramuscular). Both VOLULYTE® and 6% HES 130/0.4 in 0.9% sodium chloride solution showed good local tolerance in rabbits after intravenous infusion and also indicated no difference between both HES solutions.

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PART III: CONSUMER INFORMATION

VOLULYTE®

6% hydroxyethyl starch 130/0.4 in an isotonic electrolyte injection

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

ABOUT THIS MEDICATION

What the medication is used for:

VOLULYTE® is a plasma volume substitute that is used in adults to restore the blood volume when you have lost blood. It is used when other products called crystalloids are not considered sufficient to be used alone to restore your blood volume. VOLULYTE® is not a substitute for red blood cells or clotting factors in plasma.

What it does:

VOLULYTE® belongs to a group of medicines known as plasma volume expanders. VOLULYTE® works for several hours by increasing the volume of circulating blood.

When it should not be used:

Your doctor will not administer VOLULYTE® if:

- you have too much fluid in your body
- you have a serious generalized infection
- you have been told that you have pulmonary edema where too much fluid is in your lungs
- you are critically ill (e.g. you need to stay in an intensive care unit)
- you have been told that you have congestive heart failure (a condition in which your heart cannot pump enough blood to other organs of your body)
- you have pre-existing blood clotting or bleeding disorders
- you have kidney impairment and you produce little or no urine and if this is not caused by low blood volume
- you are receiving dialysis treatment (an artificial kidney treatment)
- you have severe liver disease
- you suffer from bleeding within or around the brain (intracranial bleeding)
- you have severely elevated levels of either potassium, sodium or chloride in your blood.
- you are allergic (hypersensitive) to hydroxyethyl starch or any of the other ingredients.

What the medicinal ingredient is:

6% hydroxyethyl starch 130/0.4 in an isotonic electrolyte injection.

What the non-medicinal ingredients are:

Magnesium chloride hexahydrate, Potassium chloride, Sodium acetate trihydrate, Sodium chloride, Water for injections; pH adjusted with sodium hydroxide or hydrochloric acid.

What dosage form it comes in:

Solution (for infusion): 6% hydroxyethyl starch 130/0.4 in an isotonic electrolyte injection supplied in 250 ml and 500 ml plastic bags.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The use of hydroxyethyl starch (HES) products, including VOLULYTE in critically ill patients, including patients with sepsis increases the risk of death and for renal (kidney) replacement therapy.

HES products, including VOLULYTE should not be given in critically ill patients, including patients with sepsis.

BEFORE VOLULYTE® is administered to you talk to your doctor or nursing staff if:

- You have heart or kidney problems.
- You have bleeding disorders.

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, electrolytes in your blood and fluid balance to maintain adequate hydration. Your doctor will be particularly careful if you have elevated levels of potassium, sodium, magnesium, or chloride in your blood. Your doctor regularly monitors your liver function.
- If your kidney function shows signs of problems during therapy, your doctor will stop giving you this medicine. If, for other reasons you are in hospital for long-term, your doctor may need to monitor your kidney function for up to 90 days.
- If you are given this medicine repeatedly or in open heart surgery your doctor will monitor the ability of your blood to clot. If it shows signs of problems during therapy your doctor will stop giving you this medicine.
- This medicine may temporarily increase the level of the enzyme serum amylase and could interfere with the diagnosis

of inflammation of the pancreas (pancreatitis).
- Itching or allergic reactions to VOLULYTE® may occur.
- Tell your doctor about any unusual symptoms that you develop.

Use in Pregnancy
VOLULYTE® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women
It is not known whether VOLULYTE® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VOLULYTE® is being considered for a nursing mother.
You and your doctor must decide whether to continue/discontinue breast-feeding or to discontinue/continue therapy with VOLULYTE® by taking into account the benefit of breast-feeding to the child and the benefit of VOLULYTE® therapy to the nursing mother.

INTERACTIONS WITH THIS MEDICATION

It is not known if VOLUVEN interacts with other medications.

Some medicinal products can cause potassium or sodium retention when taken at the same time as VOLULYTE®. Tell your doctor all the medications you are taking including prescription, non-prescription and natural health products.

PROPER USE OF THIS MEDICATION

VOLULYTE® is given to you by your doctor. Your doctor will decide the best dose for you and for how long you will need to be treated with VOLULYTE.

It is given by injection into your vein as an infusion (intravenous infusion).

Overdose:

In case of drug overdose, your doctor will stop the infusion immediately and, if necessary, administer therapies that remove water from the body and may contact the regional Poison Control Centre immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

- Itching
- Abnormal blood test results, such as decrease of hematocrit or plasma proteins
- The level of serum amylase can rise during administration of VOLULYTE® and can interfere with the diagnosis of inflammation of the pancreas (pancreatitis); however, VOLULYTE® does not cause pancreatitis.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or nursing staff		Doctor will stop treatment
		Only if severe	In all cases	
Rare	Allergic reactions with symptoms such as mild flu- like symptoms; i.e. fever, headache, slow heartbeat, fast heartbeat, bronchitis, fluid in the lungs unrelated to heart problems.		√	√
	Unusual bruising or bleeding		√	√

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

HOW TO STORE IT

VOLULYTE is stored by your healthcare professional.
Store: **free***flex*® bag at 15 °C – 25 °C
The product should be used immediately after opening. Do not freeze.
Do not use VOLULYTE® after expiry date.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

IF YOU WANT MORE INFORMATION ABOUT VOLULYTE®

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada Website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website (http://www.fresenius-kabi.ca), or by calling 1-877-821-7724 (toll-free-telephone).

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