NON ANNOTATED VERSION

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Voluven® safely and effectively. See full prescribing information for Voluven®.

Voluven® (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection)
For administration by intravenous infusion
Initial U.S. Approval: 2007

----------INDICATIONS AND USAGE----------

Voluven® is a plasma volume substitute indicated for the treatment and prophylaxis of hypovolemia in adults and children. (1)

----------DOSAGE AND ADMINISTRATION----------

Administer by intravenous infusion only.

- Daily dose and rate of infusion depend on the patient's blood loss, hemodynamics and on the hemodilution effects. (2)

	Recommended Daily Dose
Adults (2.1)	Up to 50 mL/kg body weight

	Recommended Daily Dose	**Mean Daily Dose ± SD in Clinical Trials (2.2)**
Pediatric age groups (2.2)	Up to 50 mL/kg body weight in all age groups	-
< 2 years		16 ± 9 mL/kg body weight
2 – 12 years		36 ± 11 mL/kg body weight
> 12 years		-

- Initiate infusion slowly due to possible anaphylactoid reactions (2, 5.1)
- See full prescribing information for pediatric administration (2.2, 8.4)

----------DOSAGE FORMS AND STRENGTHS----------

500 mL **free***flex*® flexible plastic intravenous solution container. Each 100 mL contains 6 g hydroxyethyl starch 130/0.4 in isotonic sodium chloride injection. (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to hydroxyethyl starch (4)
- Fluid overload e.g., pulmonary edema and congestive heart failure (4)
- Renal failure with oliguria or anuria not related to hypovolemia (4)
- Patients receiving dialysis (4)
- Severe hypernatremia or severe hyperchloremia (4)

- Intracranial bleeding (4)

----------WARNINGS AND PRECAUTIONS----------

- Anaphylactoid and hypersensitivity reactions (5.1, 6)
- Avoid fluid overload; adjust dosage in patients with cardiac or renal dysfunction (5.1)
- In severe dehydration, a crystalloid solution should be given first (5.1)
- Monitor liver functions and coagulation parameters in patients with severe liver disease or bleeding disorders (5.1)
- Monitor kidney function, fluid balance and serum electrolytes (5.2)
- Elevated serum amylase values may occur and interfere with the diagnosis of pancreatitis (5.3)
- High dosages may cause dilution of blood components (5.3)

----------ADVERSE REACTIONS----------

Anaphylactoid/hypersensitivity reactions can occur. Most common adverse reactions (incidence >1%) are pruritus, elevated serum amylase, hemodilution (resulting in dilution of blood components, e.g., coagulation factors and other plasma proteins, and in a decrease in hematocrit). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Hospira Inc. at 1-800-441-4100 or electronically at ProductComplaintsPP@hospira.com or FDA at 1-800-FDA-1088 or electronically at www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

No interactions with other drugs or nutritional products are known. (7)
The safety and compatibility of additives have not been established.

----------USE IN SPECIFIC POPULATIONS----------

- Pediatric patients: Dosage should be adjusted to individual patient needs. (2.2, 8.4)
- Renal impaired or geriatric patients: Dose adjustment needed dependent on patient´s status. (8.5, 8.6)

See 17 for PATIENT COUNSELING INFORMATION**.**
Issued: May 2, 2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Voluven® (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection) is indicated for the treatment and prophylaxis of hypovolemia in adults and children. It is not a substitute for red blood cells or coagulation factors in plasma.

2 DOSAGE AND ADMINISTRATION

Voluven® is administered by intravenous infusion only. The daily dose and rate of infusion depend on the patient's blood loss, on the maintenance or restoration of hemodynamics and on the hemodilution (dilution effect). Voluven® can be administered repetitively over several days. [see *Warnings and Precautions (5)*]

The initial 10 to 20 mL should be infused slowly, keeping the patient under close observation due to possible anaphylactoid reactions. [see *General Warnings and Precautions (5.1)*]

2.1 Adult Dose

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

2.2 Pediatric Dose

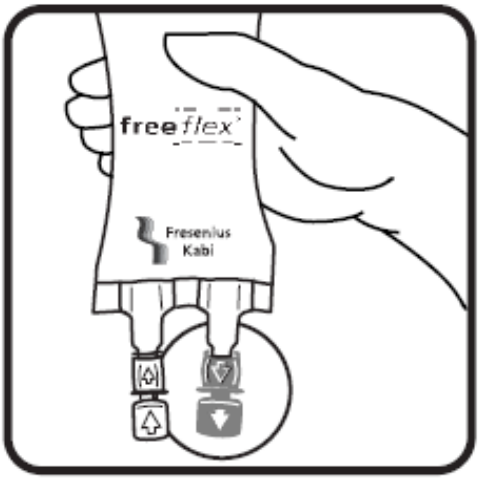
The dosage in children should be adapted to the individual patient colloid needs, taking into account the disease state, as well as the hemodynamic and hydration status.

In 41 newborns to infants (< 2 years), a mean dose of 16 ± 9 mL/kg was administered. In 31 children from 2 – 12 years of age a mean dose of 36 ± 11 mL/kg was administered. The dose in adolescents > 12 is the same as the adult dose. [see *Pediatric Use (8.4)*]

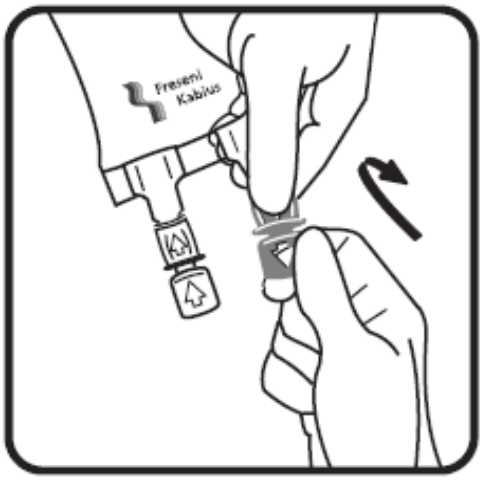
136 **2.3 Directions for Use of Voluven®**

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

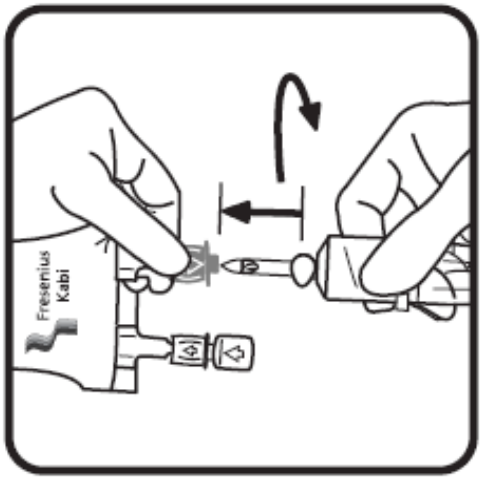
- Use opening aid to remove over-wrap.



- Identify the blue infusion (administration) port.



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



- Close roller clamp. Insert the spike until the clear plastic collar of the port meets the shoulder of the spike.
- Use a non-vented standard infusion set.
- Close air inlet.

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

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. Voluven® should be used immediately after insertion of the administration set.
5. Do not vent.
6. If administered by pressure infusion, air should be withdrawn or expelled from the bag through the medication/administration port prior to infusion.
7. Discontinue the infusion if an adverse reaction occurs.
8. It is recommended that administration sets be changed at least once every 24 hours.
9. For single use only. Discard unused portion.

3 DOSAGE FORMS AND STRENGTHS

500 mL **free***flex*® flexible plastic intravenous solution container are available. Each 100 mL contains 6 g hydroxyethyl starch 130/0.4 in isotonic sodium chloride injection.

4 CONTRAINDICATIONS

The use of Voluven® is contraindicated in the following conditions:

- known hypersensitivity to hydroxyethyl starch [see *General Warnings and Precautions (5.1)*]
- fluid overload (hyperhydration) and especially in cases of pulmonary edema and congestive heart failure
- renal failure with oliguria or anuria not related to hypovolemia
- patients receiving dialysis treatment
- severe hypernatremia or severe hyperchloremia
- intracranial bleeding.

5 WARNINGS AND PRECAUTIONS

5.1 General Warnings and Precautions

Anaphylactoid reactions (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. [see *Adverse Reactions (6)*]

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

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

Monitor liver function and coagulation parameters when administering Voluven® to patients with severe liver disease or severe bleeding disorders (e.g., severe cases of von Willebrand´s disease).

5.2 Monitoring: Laboratory Tests

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

5.3 Interference with Laboratory Tests

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

At high dosages the dilutional effects may result in decreased levels of coagulation factors and other plasma proteins and a decrease in hematocrit.

6 ADVERSE REACTIONS

6.1 Overall Adverse Reaction Profile

The most common adverse reactions after administration of Voluven® occurring in more than 1% of patients are: pruritus (itching; ≥1% to <10%), elevation of serum amylase (≥1% to <10%; can interfere with the diagnosis of pancreatitis), and dilutional effects that may result in decreased levels of coagulation factors and other plasma proteins and in a decrease of hematocrit (≥1% to <10%).

Anaphylactoid reactions occur rarely in <0.1% after administration of hydroxyethyl starch solutions. Furthermore, with the administration of hydroxyethyl starch solutions, disturbances of blood coagulation beyond dilution effects can occur rarely in <0.1% depending on the dosage[2].

6.2 Adverse Reactions in Clinical Trials

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug may not reflect the rates observed in practice.

During clinical development, a total of 899 subjects received the hydroxyethyl starch 130/0.4 drug substance contained in Voluven at different concentrations (2%, 4%, 6%, or 10%) and at cumulative doses of several mL up to 66 L[1]. Of these 899 subjects, 602 were exposed to Voluven® (i.e., 6% hydroxyethyl starch 130/0.4). The mean duration of treatment with hydroxyethyl starch 130/0.4 was 3.7 ± 3.1 days, mean cumulative doses were 3185 ± 3498 mL, and the longest follow-up period was 90 days.

In 100 subjects undergoing elective orthopedic surgery Voluven® was administered in 49 subjects and hetastarch (6% hydroxyethyl starch in 0.9% sodium chloride injection) in 51 subjects for intraoperative volume replacement. Mean infusion volumes were 1613 ± 778 mL for Voluven® and 1584 ± 958 mL for hetastarch.

Adverse reactions observed in at least 1% of subjects: In the orthopedic surgery trial conducted in the US, no significant differences in serious adverse reactions were noted overall between the two treatment arms. A possible relationship to Voluven® was reported in five cases among three subjects (aPTT elevated, PT prolonged, wound hemorrhage, anemia, pruritus). A possible relationship to hetastarch was reported in five subjects (three cases of coagulopathy; two cases of pruritus). The three coagulopathy cases in the hetastarch group were serious and occurred in subjects receiving more than the labeled ceiling dose (20 mL/kg), which is known to increase the risk of bleeding, whereas no serious coagulopathy occurred in the Voluven® group. Since EBL for the two treatment arms was not statistically different (95% confidence interval included unity), the difference observed for Factor VIII (see Table 1, below) must be interpreted with caution. An exploratory analysis of total erythrocyte volume transfused (8.0 mL/kg vs. 13.8 mL/kg, Voluven® vs. hetastarch, respectively) must also be viewed with caution.

Table 1: Safety Variables for the Orthopedic Surgery Trial conducted in the US

	Mean		Ratio VOLUVEN/Hetastarch	
Variable	**VOLUVEN N=49**	**Hetastarch N=51**	**Estimate**	**95% Cl**
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]

*****Exploratory analyses

A safety profile of Voluven® at least as favorable as for pentastarch was also demonstrated in studies where Voluven® was administered at doses higher (up to 50 mL/kg or 3 g/kg) than for pentastarch (up to 33 mL/kg or 2 g/kg) in clinical settings where large or repetitive doses were administered.

6.3 Postmarketing Experience

The following adverse reactions have been identified during the post-approval use of Voluven® and other types of hydroxyethyl starch solutions. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Among the very rarely occurring serious adverse drug reactions in patients treated with Voluven®, anaphylactic/anaphylactoid/hypersensitivity reactions or hypotension/shock/ circulatory collapse were most frequently reported.

7 DRUG INTERACTIONS

The safety and compatibility of other additives have not been established.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Voluven® has been shown to cause embryocidal or other adverse effects in rats and rabbits when given in doses 1.7 times the human dose.

The type of hydroxyethyl starch present in Voluven® had no teratogenic properties in rats or rabbits. At 5 g/kg of body weight per day, administered as a bolus injection, fetal retardations and embryolethal effects were observed in rats and rabbits, respectively. In rats, a bolus injection of this dose during pregnancy and lactation reduced body weight of offspring and induced developmental delays. All adverse effects were seen exclusively at maternal toxic doses due to fluid overload. [see *Toxicology (13.2.1)*]

Fertility studies on directly exposed animals have not been conducted.

There are no adequate and well-controlled studies in pregnant women. Voluven® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

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

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Voluven® is administered to a nursing woman.

8.4 Pediatric Use

In one trial, newborns and infants < 2 years of age undergoing elective surgery were randomized to receive Voluven® (N=41) or 5% albumin (N=41). The mean dose of Voluven® administered was 16 ± 9 mL/kg.

In an additional trial, children from 2 – 12 years of age undergoing cardiac surgery were randomized to receive Voluven® (N=31) or 5% albumin (N=30). The mean dose administered was 36 ± 11 mL/kg.

Use of Voluven® in adolescents > 12 years is supported by evidence from adequate and well-controlled studies of Voluven® in adults.

Dosage in children should be adapted to individual patient colloid needs, taking into account underlying disease, hemodynamics and hydration status. [see *Pediatric Dose (2.2)*]

8.5 Geriatric Use

Of the total number of subjects in clinical studies of Voluven® (N=471), 32% were ≥ 65 years old while 7% were ≥ 75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

Voluven® is mainly excreted by the kidneys, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Volume status, infusion rate, and urine output should be closely monitored. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. [see *Pharmacokinetics (12.3)*]

10 OVERDOSAGE

Overdosage 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. [see *General Warnings and Precautions (5.1)*]

11 DESCRIPTION

Voluven® (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection) is a clear to slightly opalescent, colorless to slightly yellow, sterile, non-pyrogenic, isotonic solution for intravenous administration using sterile equipment.

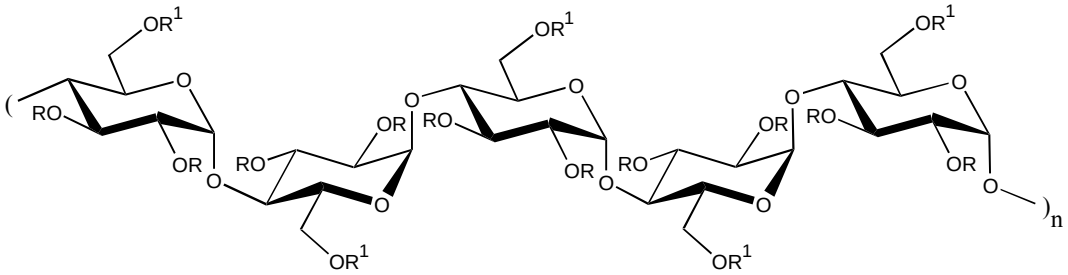
Each 100 mL of the solution contains: 6 g of Hydroxyethyl Starch 130/0.4 and 900 mg of Sodium Chloride USP in Water for Injection USP.

In addition, sodium hydroxide, USP, or Hydrochloric acid, USP, has been added to adjust the final pH so the final solution pH is 4.0 to 5.5.

The electrolyte composition is as follows (mEq/L): Sodium 154, Chloride 154.

The calculated osmolarity is 308 mOsmol/L.

The hydroxyethyl starch contained in Voluven® is a synthetic colloid for use in plasma volume replacement. The chemical name of hydroxyethyl starch is poly(O-2-hydroxyethyl) starch. The structural formula of hydroxyethyl starch is



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

Voluven® is packaged in 500 mL flexible plastic containers (**free***flex*®). **Free***flex*® is a flexible container made from coextruded polyolefin and is free of PVC, plasticizers, adhesives or latex (Non-DEHP, Latex-free). The **free***flex*® container offers an air-closed system and can be used with non-vented IV sets which prevent external air contamination. **Free***flex*® is collapsible and can be used in emergency cases for pressure infusion.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Voluven® contains hydroxyethyl starch in a colloidal solution which expands plasma volume when administered intravenously. This effect depends on the mean molecular weight (130,000 daltons; range 110,000 – 150,000 daltons), the molar substitution by hydroxyethyl groups (0.4; range 0.38 – 0.45) on glucose units of the starch, the pattern of hydroxyethyl substitution (C_2/C_6 ratio) of approximately 9:1, and the concentration (6%), as well as the dosage and infusion rate.

Hydroxyethyl starch is a derivative of thin boiling waxy corn starch, which mainly consists of a glucose polymer (amylopectin) predominantly composed of α-1-4-connected glucose units with several α-1-6-branches. Substitution of hydroxyethyl groups on the glucose

units of the polymer reduces the normal degradation of amylopectin by α-amylase in the body. The low molar substitution (0.4) is the main pharmacological determinant for the beneficial effects of Voluven® on pharmacokinetics, intravascular volume and hemodilution[4]. To describe the molecular weight and molar substitution characteristics of the hydroxyethyl starch in Voluven®, the compound is designated as hydroxyethyl starch 130/0.4.

12.2 Pharmacodynamics

After isovolemic exchange of blood with 500 mL of Voluven® in healthy volunteers, blood volume is maintained for at least 6 hours.

12.3 Pharmacokinetics

The pharmacokinetic profile of hydroxyethyl starch is complex and largely dependent on its molar substitution as well as its molecular weight[4]. When administered intravenously, molecules smaller than the renal threshold (60,000-70,000 daltons) are readily and rapidly excreted in the urine, while molecules with higher molecular weights are metabolized by plasma α-amylase prior to excretion via the renal route.

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

Following intravenous administration of 500 mL Voluven® to healthy volunteers, plasma levels of Voluven® remain at 75% of peak concentration at 30 minutes post-infusion and decrease to 14% at 6 hours post-infusion. Plasma levels of Voluven® return to baseline levels 24 hours following infusion. Plasma clearance, volume of distribution, and elimination half-life of Voluven® in healthy volunteers following IV administration of 500 mL were 31.4 mL/min, 5.9 liters, and 12 hours, respectively. Approximately 62 % of Voluven® was excreted as hydroxyethyl starch molecules in urine within 72 hours.

The pharmacokinetics 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 hydroxyethyl starch 130/0.4 over a period of 10 days. Approximately 70% of Voluven® was excreted as hydroxyethyl starch molecules in urine within 72 hours.

Renal Impairment:

Following a single intravenous administration of Voluven® (500 mL) in subjects with varying degrees of renal dysfunction, the AUC and clearance of Voluven® increased by 73% and decreased by 42% in subjects, respectively, with creatinine clearance < 50 mL/min as compared to subjects with creatinine clearance > 50 mL/min. However, terminal half-life and peak hydroxyethyl starch concentration were not affected by renal impairment. Plasma levels of Voluven® returned to baseline levels 24 hours following infusion. Approximately 59 % and 51 % of Voluven® were excreted as hydroxyethyl starch molecules in urine within 72 hours in subjects with creatinine clearance ≥30 mL/min and <30 mL/min, respectively[5].

There are no data available on the use of Voluven® in subjects undergoing hemodialysis.

Pharmacokinetic data in patients with hepatic insufficiency or in pediatric or geriatric patients are not available. Effects of gender or race on the pharmacokinetics of Voluven® have not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of Voluven® have not been performed. No mutagenic effects were observed with hydroxyethyl starch 130/0.4 10% solution in the following tests on mutagenic activity: *Salmonella typhimurium* reverse mutation assay (*in vitro*), mammalian cells in the *in vitro* gene mutation assay, assessment of the clastogenic activity in cultured human peripheral lymphocytes (*in vitro*), bone marrow cytogenetic test in Sprague-Dawley rats.

Fertility studies on directly exposed animals have not been performed.

13.2 Animal Toxicology and Pharmacology

13.2.1 Toxicology

Three-month repeat infusion toxicology studies were conducted in rats and dogs in which three groups of animals were administered daily intravenous infusion over three hours. Dosing volumes of either 60 or 90 mL/kg body weight of hydroxyethyl starch 130/0.4 (10% solution) or 90 mL/kg 0.9% sodium chloride injection were studied. Observed toxicity following repeat infusion of hydroxyethyl starch is consistent with the oncotic properties of the solution resulting in hypervolemia in the animals. There were no gender-related effects on toxicity following repeat administration of hydroxyethyl starch 130/0.4 in rats or dogs.

In reproduction studies in rats and rabbits, hydroxyethyl starch 130/0.4 (10% solution) had no teratogenic properties. Embryolethal effects were observed in rabbits at 5 g/kg body weight/day. In rats, bolus injection of this dose during pregnancy and lactation reduced body weight of offspring and induced developmental delays. Signs of fluid overload were seen in the dams. Hydroxyethyl starch 130/0.4 (10% solution) had no effect in studies assessing skin sensitization, antigenicity, and blood compatibility.

13.2.2 Pharmacology

The pharmacodynamic effect of Voluven® was examined in a hemorrhagic shock model in conscious rats and a hemodilution model in dogs. In both studies the control group received pentastarch (6% hydroxyethyl starch 200/0.5).

Voluven® was as effective as pentastarch in maintaining cardiopulmonary function during isovolemic hemodilution in beagle dogs. In the three-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 Voluven® and pentastarch solutions following induced hemorrhagic shock (67% and 50% blood loss). In the 67% induced bleeding group receiving Voluven® (N=6), the survival rate was 83% which is within the normal range for this type of experiment. In the corresponding pentastarch 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.

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

A study with 10% radiolabeled ^{14}C-hydroxyethyl starch 130/0.4 and 10% ^{14}C-hydroxyethyl starch 200/0.5 solutions was carried out[6]. In animals treated with hydroxyethyl starch 130/0.4, radioactivity decreased from 4.3% of the total administered dose (2.6 g hydroxyethyl starch 130/0.4 per animal) on day 3 to 0.65% on day 52. In animals treated with hydroxyethyl starch 200/0.5, the ^{14}C-activity decreased from 7.7% of the total administered dose (2.7 g hydroxyethyl starch 200/0.5 per animal) on day 3 to 2.45% on day 52. These results confirm the faster elimination and lower persistence of hydroxyethyl starch 130/0.4 in tissue.

14 CLINICAL STUDIES

Voluven® was studied in controlled clinical trials among adult and pediatric subjects undergoing various types of surgery (orthopedic, urologic, cardiac) in which hypovolemia is treated (pre-, intra-, and postoperative) or prevented (autologous blood donation, acute normovolemic hemodilution, hypervolemic hemodilution before cardiac surgery). Adult subjects in intensive care units also were studied. The safety and efficacy of Voluven® were compared to other colloidal plasma substitutes [pentastarch (6% hydroxyethyl starch 200/0.5), hetastarch (6% hydroxyethyl starch 450/0.7), gelatin solution or human serum albumin]. Perioperative fluid administration of Voluven® ranged from 500 to 4500 mL/day in surgical subjects, and cumulatively, from 6 to 66 L in intensive care subjects following traumatic brain injury.

Orthopedic surgery trial

A prospective, controlled, randomized, double-blind, multi-center trial of 100 subjects undergoing elective orthopedic surgery was conducted in the US evaluating Voluven® (N=49) compared to hetastarch (6% hydroxyethyl starch in 0.9% sodium chloride injection) (N=51) for intraoperative volume replacement therapy[7]. The primary efficacy variable, total volume of colloid solution required for intraoperative volume replacement therapy, was equivalent for the two treatment groups. Mean volume infused 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), which was included within the equivalence range of (0.55, 1.82) prespecified in the study protocol. This indicated that Voluven® and hetastarch have similar efficacy as intraoperative volume replacement therapy in major orthopedic surgery.

A second objective of the trial was to show superiority for safety between Voluven® and hetastarch. Four safety endpoints were prospectively defined and compared in a sequential manner (in order to preserve the type-1 error rate, i.e., observing a difference where none actually exists). Per protocol, if there was no difference found between treatment arms for the first safety endpoint (EBL), the remaining endpoints were to be considered exploratory analyses requiring additional studies for confirmation. [see *Adverse Reactions in Clinical Trials (6.2)*]

There was no statistically significant difference between the two treatment groups with respect to the secondary efficacy endpoints of hemodynamic stability, body temperature, hemodynamic parameters, blood pressure, central venous pressure, heart rate, fibrinogen and platelet count.

In addition to the US trial, three non-US trials were conducted with the primary objective of showing equivalency (based on mean difference rather than mean ratio as in the US study) between Voluven® and pentastarch in maintaining or restoring hemodynamic parameters. The largest of the three trials (N=100) met the prespecified boundary (-500 mL, 500 mL), but the two smaller studies (N=52 and N=59) did not.

In exploratory analyses, the effect of Voluven® on coagulation parameters (von Willebrand factor, Factor VIII, and Ristocetin cofactor) was shown to be significantly lower than pentastarch at one or more time points (US and non-US trials). These findings are consistent with the lower molar substitution, lower average molecular weight and narrower molecular weight distribution of Voluven® as compared to pentastarch resulting in a lower *in vivo* molecular weight and increased elimination from the circulation.

Severe sepsis trial

A randomized, double-blind, multicenter study of subjects with severe sepsis ≥ 18 years old compared Voluven® (n=100) vs. normal saline (n=96) infused over a maximum of 4 days for the treatment of hypovolemia. The primary endpoint was volume of study drug (mL) required to achieve initial hemodynamic stabilization (HDS), defined as MAP ≥ 65 mmHg, CVP 8-12 mmHg, urine output ≥ 2 mL/kg over 4 h, and central venous oxygen saturation ≥ 70% maintained for four hours with no increase in the infusion rate of vasopressors or inotropic support and ≤ 1 L of additional study drug administration. Safety parameters included the incidence of acute renal failure, prospectively defined as need for renal replacement therapy (RRT) or doubling of baseline serum creatinine at some point during the 90-day observation period. AKIN and RIFLE criteria also were evaluated.

Baseline characteristics for the two treatment arms were 24.0% vs. 18.8% for intra-abdominal sepsis, 53.0% vs. 60.4% for pulmonary sepsis, and 8.0% vs. 14.6% for urogenital sepsis, Voluven® vs. normal saline, respectively.

Subjects achieving HDS (N=88 vs. 86) required less Voluven® compared to control: 1379 mL ± 886 (Voluven®) vs. 1709 ± 1164 mL (normal saline), representing a mean difference of 331 mL (95% confidence interval: -640 mL to -21 mL). Less time was needed from start of study drug to achievement of HDS in the Voluven® group compared to the normal saline group (11.8 hours ± 10.1 hours vs. 14.3 hours ± 11.1 hours; mean ± SD).

A *post hoc* sensitivity analysis was performed to determine the number of subjects not achieving HDS as a result of a change made to the protocol definition of HDS after enrollment had commenced, i.e., from requiring all four hemodynamic criteria to requiring normalization of MAP and two of the three remaining hemodynamic criteria. Approach 1 used the original definition of HDS for subjects enrolled prior to the protocol change and the revised definition of HDS for subjects enrolled subsequently; Approach 2 used the revised definition of HDS for all enrolled subjects. More Voluven® subjects than control subjects were declared to have achieved HDS, although not all the requirements for HDS had been fulfilled (see Table 2).

Table 2: *Post Hoc* Sensitivity Analysis

	Voluven (N=100) n (%)	Normal saline (N=96) n (%)	p-value
Number of subjects without declaration of HDS	12 (12.0)	10 (10.4)	0.3628
Number of subjects without declaration of HDS plus number of subjects with HDS declared by Approach 1	25 (25.0)	18 (18.8)	0.1453
Number of subjects without declaration of HDS plus number of subjects with HDS declared by Approach 2	22 (22.0)	16 (16.7)	0.1725

The number of treatment emergent serious adverse events (SAEs) and the number of treatment emergent SAEs leading to death in the Voluven® and normal saline treatment arms during the 90-day observation period were 53 vs. 44 and 38 vs. 32, respectively.

Acute kidney injury scores (AKIN and RIFLE classifications) were comparable between groups (see Table 3, below). The number of subjects undergoing RRT was 21 vs. 11 for the 90-day observation period and ***17*** ~~16~~ vs. ***8*** ~~7~~ for the first 7 days of treatment. Mean duration of RRT was 9.1 days in the Voluven® arm vs. 4.3 days in the normal saline arm.

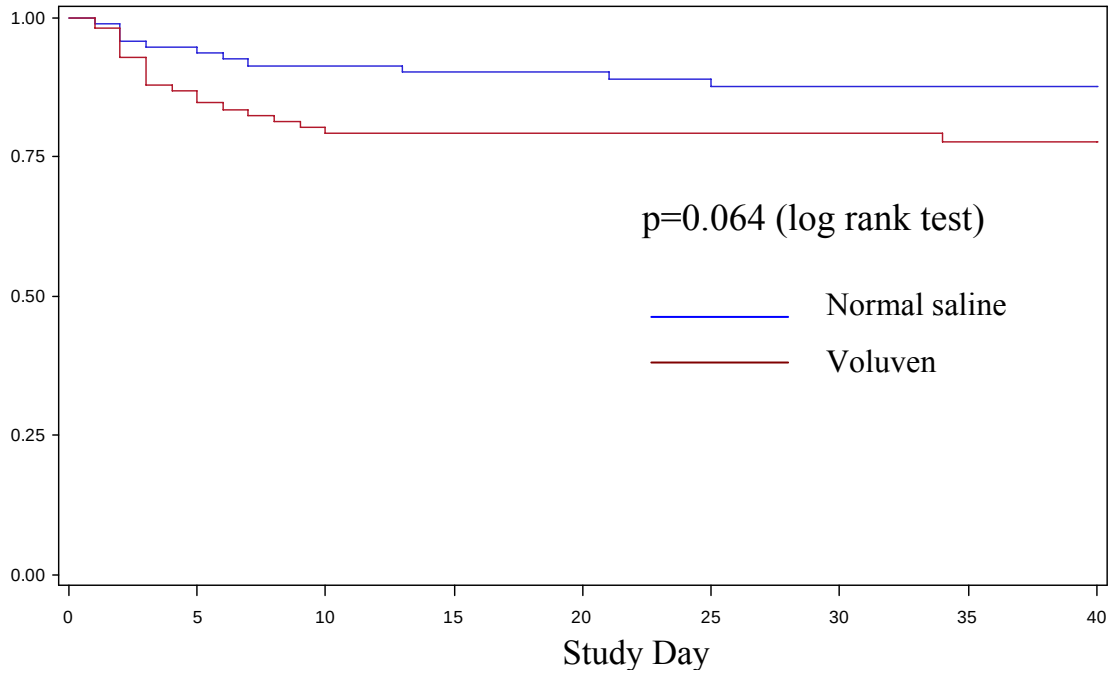
Kaplan-Meier curves for time to RRT (Figure 1, below) showed a trend against Voluven® (p=0.06, log-rank test) [see 6. Adverse Reactions].

Table 3: Evaluation of Subjects According to the AKIN Classification

Worst AKIN Stage	Voluven (N=100) m	n (%)		Normal saline (N=96) m	n (%)
None	100	52 (52.0)		96	52 (54.2)
AKIN Stage 1	100	21 (21.0)		96	21 (21.9)
AKIN Stage 2	100	5 (5.0)		96	6 (6.3)
AKIN Stage 3	100	22 (22.0)		96	17 (17.7)
p-value of test for trend			0.5857		

AKIN classification was based on serum creatinine values and renal replacement therapy. Urine output criteria were ignored. Percentages are based on the number of evaluable subjects (m), i.e., the number of subjects for whom an AKIN score could be determined.

Figure 1: Kaplan-Meier Curves for time to RRT



15 REFERENCES

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16 HOW SUPPLIED/STORAGE AND HANDLING

Voluven® (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection) for intravenous infusion is supplied in the following primary container and carton sizes:

Polyolefin bag (**free***flex*®) with overwrap: 500 mL

Carton of 15 x 500 mL

NDC 0409-1029-01

Carton of 20 x 500 mL

NDC 0409-1029-02

Store at 15° to 25°C (59° to 77°F). Do not freeze.

17 PATIENT COUNSELING INFORMATION

Because this product is not used directly by patients, patient counseling or instructions for use by patients is not considered necessary.

Manufactured by: Fresenius Kabi Norge AS,
P.O. Box 430,
NO-1753 Halden, Norway

Distributed by:
Hospira, Inc.
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Lake Forest, Illinois 60045 USA

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