FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Voluven® (16% hydroxyethyl starch 130/0.4 in isotonic sodium chloride injection) is indicated for the treatment and prophylaxis of hypovolemia. 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, hemodynamics and on the hemodilution (dilution effect). Voluven® can be administered repetitively over several days. (SeeWarnings and Precautions(5.2).)

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 of hydroxyethyl starch) may be administered. 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 hematopoietic status. The safety and efficacy of Voluven® have not been established in the age group of 2 to 12 years. Use of Voluven® in children ≥12 years is supported by evidence from adequate and well-controlled studies of Voluven® in adults and by data from children <2 years old. (See Pediatric Use(8.4).

2.2 Pediatric Dose

Limited clinical data on the use of Voluven® in children are available. In 41 children including newborns to infants (<2 years), a mean dose of 18 ± 9 mL/kg was administered. The dosage in children should be adapted to the individual patient needs in order to create a disease state, as well as the hemodynamic and hematopoietic status. (See General Warnings and Precautions(5.1).)

The safety and efficacy of Voluven® have not been established in the age group of 2 to 12 years. Use of Voluven® in children ≥12 years is supported by evidence from adequate and well-controlled studies of Voluven® in adults and by data from children <2 years old. (See Pediatric Use(8.4).

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.
- Identify the blue infusion (administration) port.
- Break off the blue tamper-evident cover from the free® infusion port.
- Hang the bag on the infusion stand. Press drip chamber to get fluid level. Prime infusion set. Connect and adjust the flow rate.

3 OVERDOSAGE

3.1 General Warnings and Precautions

- Monitor kidney function, fluid balance and serum electrolytes (5.2).
- High doses may cause dilution of blood components (5.3).

3.2 Dosage in Children

- Use a non-vented standard infusion set.
- The following adverse reactions have been identified during the post-approval experience of Voluven®. (See Adverse Reactions(6).

3.3 Use in Pregnant Women

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.

4 CONTRAINDICATIONS

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

- Known hypersensitivity to hydroxyethyl starch (4).
- Severe hypernatremia or severe hyperchloremia (4).
- Renal failure with oliguria or anuria not related to hypovolemia (4).
- Pancreatitis (5.3)
- Use opening aid to remove over-wrap.
- Intracranial bleeding (4).

5 WARNINGS AND PRECAUTIONS

- Anaphylactic or hypersensitivity reactions may occur. Most common adverse reactions (incidence >1%) are pruritus, elevated serum amylase, hemolysis (resulting in dilution of blood components, e.g., coagulation factors and other plasma proteins), and a decrease in hematocrit. (5.2).
- Check the solution composition, lot number and expiry date, inspect the container for damage or leakage, if damaged do not use.

6 ADVERSE REACTIONS

6.1 Overall Adverse Reaction Profile

In the US trial, 100 patients undergoing elective orthopedic surgery were treated either with Voluven® (N=98) or hetastarch (6% hydroxyethyl starch in 0.9% sodium chloride injection) (N=51) for intraoperative volume replacement. Mean infusion volumes were 1813 ± 770 mL for Voluven® and 1904 ± 588 mL for hetastarch.

6.2 Adverse Reactions in Clinical Trials

During clinical development, 471 patients were exposed to Voluven®, and a total of 798 patients received the hydroxyethyl starch 130/0.4 drug substance contained in Voluven® at different concentrations (2%, 4%, 6%, 8%) and at cumulative doses of several mL up to 64 L. The mean duration of treatment with hydroxyethyl starch 130/0.4 was 3.9 ± 3.2 days, mean cumulative doses were 3238 ± 309 mL, and the longest follow-up period was 98 days.

In the US trial, 100 patients undergoing elective orthopedic surgery were treated either with Voluven® (N=98) or hetastarch (6% hydroxyethyl starch in 0.9% sodium chloride injection) (N=51) for intraoperative volume replacement. Mean infusion volumes were 1813 ± 770 mL for Voluven® and 1904 ± 588 mL for hetastarch.

Adverse reactions observed in at least 1% in patients: In the US trial comparing Voluven® with hetastarch, a possible relationship to Voluven® was reported in five cases in a total of three patients (3%) of coagulopathy, two cases of pruritus. The three coagulopathy cases in the hetastarch group were serious and occurred in patients receiving more than the labeled ceiling dose (30 mL/kg), whereas no serious coagulopathy occurred in the Voluven® group.

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.

The safety profile from postmarketing experience of Voluven® is not different from the profile obtained from clinical trials performed using the product. Based on spontaneous reporting of hypersensitivity reactions, urticaria, bronchospasm, or hypertension were the most frequently reported serious adverse drug reactions for patients treated with Voluven®.

With the administration of hydroxyethyl starch solutions, disturbances of blood coagulation can occur depending on the dosage.

7 DRUG INTERACTIONS

No interactions with other drugs or nutritional products are known. (7)

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. 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 Lactation

There are no adequate and well-controlled studies in women. Voluven® is excreted in the milk of rats, and therefore, it is not known whether Voluven® is excreted in human milk. Because many drugs are excreted in human milk, the physician should weigh the potential benefits of Voluven® against the potential risks of its use in a nursing woman.

8.3 Children

Studies of Voluven® in adults and by data from children <2 years old. (See Pediatric Use(8.4).

8.4 Pediatric Use

- Use a non-vented standard infusion set.
- The following adverse reactions have been identified during the post-approval experience of Voluven®. (See Adverse Reactions(6).

9 DRUG ABUSE AND DEPENDENCE

There are no adequate and well-controlled studies in women. Voluven® is excreted in the milk of rats, and therefore, it is not known whether Voluven® is excreted in human milk. Because many drugs are excreted in human milk, the physician should weigh the potential benefits of Voluven® against the potential risks of its use in a nursing woman.

9.6 Dependence

There are no adequate and well-controlled studies in women. Voluven® is excreted in the milk of rats, and therefore, it is not known whether Voluven® is excreted in human milk. Because many drugs are excreted in human milk, the physician should weigh the potential benefits of Voluven® against the potential risks of its use in a nursing woman.

10 OVERDOSAGE

- Use a non-vented standard infusion set.
- The following adverse reactions have been identified during the post-approval experience of Voluven®. (See Adverse Reactions(6).

11 DESCRIPTION

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacokinetics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and Pharmacology

13.3 Animal Toxicology

14 CLINICAL STUDIES

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.
The type of hydroxyethyl starch (HES) present in Voluven® has no teratogenic properties in rats or rabbits. A 5 g/kg body weight dose, administered as a bolus injection of HES 130/0.4, caused fetal resorption in rats and rabbits, respectively. In a rat, a bolus injection of this dose during pregnancy and lactation caused a 10% decrease in body weight of offspring and induced minor developmental delays. All adverse effects were seen exclusively at maternal toxic doses due to fluid overload. Fertility studies on directly exposed animals have not been conducted.

8.2 Labor and Delivery
Information on the use of Voluven® during labor or delivery is unknown.

8.3 Nursing Considerations
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, children including newborns to infants (<2 years) undergoing elective surgery were treated, because Voluven® (N=41) at 5% albumin (N=41). The mean dose of Voluven® administered was 16 ± 9 mL/kg.

Voluven® may be given to premature infants and neonates only after a careful risk/benefit evaluation. Treatment with Voluven® may not have been established in the age group of 2 to 12 years. Use of Voluven® in children <12 years is supported by data from well-controlled studies and well-controlled studies in adults and by data from children <2 years old. Dosage in children should be adjusted to individual patient cooled needs, taking into account underlying disease, hemodynamic and hydration status. [See Pediatric Dose (2.2)]

8.5 Geriatric Use
The number of subjects in clinical studies of Voluven® (N=471), 32% were 65 years old or older and 7% were 70 and older. 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 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 (2.2)]

9 DRUG ABUSE AND DEPENDENCE
Voluven® is not considered to be a drug of abuse potential.

10 OVERDOSAGE
As with all plasma 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. [See General Warnings and Precautions (4.1)]

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, amorphous solution for intravenous infusion for use as a volume expander. Voluven® is a flexible container made from coextruded polyolefin and is free of PVC, phthalates, and rubber.