

HYDROXYETHYL STARCH IN SODIUM CHLORIDE- hydroxyethyl starch in sodium chloride injection, solution

B. Braun Medical Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use 6 % hydroxyethyl starch 130/0.4 in 0.9 % sodium chloride injection safely and effectively. See full prescribing information for 6 % hydroxyethyl starch 130/0.4 in 0.9 % sodium chloride injection.

6 % hydroxyethyl starch 130/0.4 in 0.9 % sodium chloride injection

For administration by intravenous infusion

Initial U.S. Approval: 2007

WARNING: MORTALITY RENAL REPLACEMENT THERAPY

See full prescribing information for complete boxed warning.

- In critically ill adult patients, including patients with sepsis, use of hydroxyethyl starch (HES) products, including 6 % hydroxyethyl starch 130/0.4 in 0.9 % sodium chloride injection, increases risk of
 - Mortality
 - Renal replacement therapy
- Do not use HES products, including 6 % hydroxyethyl starch 130/0.4 in 0.9 % sodium chloride injection, in critically ill adult patients, including patients with sepsis.

INDICATIONS AND USAGE

6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 EXCEL® Container. Each 100 mL contains 6 g hydroxyethyl starch 130/0.4 in isotonic sodium chloride injection. (3)

CONTRAINDICATIONS

- Do not use hydroxyethyl starch (HES) products, including 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection, in critically ill adult patients, including patients with sepsis due to increased risk of mortality and renal replacement therapy. (4)
- Do not use HES products, including 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection, in patients with severe liver disease. (4)
- Do not use HES products, including 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection, in patients with known hypersensitivity to hydroxyethyl starch. (4)
- Do not use HES products in clinical conditions with volume overload. (4)

- Do not use HES products in patients with pre-existing coagulation or bleeding disorders. (4)
- Do not use HES products in patients with renal failure with oliguria or anuria not related to hypovolemia. (4)
- Do not use HES products in patients receiving dialysis. (4)
- Do not use HES products in patients with severe hypernatremia or severe hyperchloremia. (4)
- Do not use HES products in patients with intracranial bleeding. (4)

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

- Anaphylactoid and hypersensitivity reactions (5.1, 6)
- Avoid use in patients with pre-existing renal dysfunction. (5.2)
- Discontinue use of 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection at the first sign of renal injury. (5.2)
- Continue to monitor renal function in hospitalized patients for at least 90 days as use of renal replacement therapy has been reported up to 90 days after administration of HES products. (5.2)
- Monitor the coagulation status of patients undergoing open heart surgery in association with cardiopulmonary bypass as excess bleeding has been reported with HES solutions in this population. Discontinue use of 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection at the first sign of coagulopathy. (5.3)
- Avoid fluid overload; adjust dosage in patients with cardiac or renal dysfunction (5.4)
- In severe dehydration, a crystalloid solution should be given first (5.4)
- Monitor liver function in patients receiving HES products, including 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection. (5.5)
- Monitor kidney function, fluid balance and serum electrolytes (5.5)
- Elevated serum amylase values may occur and interfere with the diagnosis of pancreatitis (5.5)
- High dosages may cause dilution of blood components (5.5)

----- **ADVERSE REACTIONS** -----

- Serious adverse reactions reported in clinical trials were increased mortality and need for renal replacement therapy in critically ill patients including sepsis.

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).

Anaphylactoid/hypersensitivity reactions can occur. (6)

To report SUSPECTED ADVERSE REACTIONS, contact B. Braun Medical Inc. at 1-800-227-2862 or FDA at 1-800-FDA-1088 or 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. (7)

----- **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**.

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FULL PRESCRIBING INFORMATION

WARNING: MORTALITY RENAL REPLACEMENT THERAPY

- **In critically ill adult patients, including patients with sepsis, use of hydroxyethyl starch (HES) products, including 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection, increases risk of**
 - **Mortality**
 - **Renal replacement therapy**
- **Do not use HES products, including 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection, in critically ill adult patients, including patients with sepsis.**

1 INDICATIONS AND USAGE

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

6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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). 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 to 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)*]

2.3 Directions for Use of EXCEL® Container

Caution: Do not use plastic container in series connection.

If administered by pressure infusion, air should be withdrawn or expelled from the bag through the medication/administration port prior to infusion.

To Open

Tear overwrap down at notch and remove solution container. Check for minute leaks by squeezing solution container firmly. If leaks are found, discard solution as sterility may be impaired.

Note: Before use, perform the following checks:

- Read the label carefully.
- Do not remove the plastic infusion container from its overwrap until immediately before use.
- While the overwrap is intact, identify the solution as 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection, the lot number, and the expiration date.
- Check that the solution is clear.
- Inspect the intact unit for signs of obvious damage. If present, the unit should not be used.
- Use only if solution is clear and container and seals are intact.

Preparation for Administration

1. Remove plastic protector from sterile set port at bottom of container.
2. Attach administration set. Refer to complete directions accompanying set.

3 DOSAGE FORMS AND STRENGTHS

500 mL EXCEL® Container is available. Each 100 mL contains 6 g hydroxyethyl starch 130/0.4 in isotonic sodium chloride injection.

4 CONTRAINDICATIONS

- Do not use hydroxyethyl starch (HES) products, including 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection, in critically ill adult patients, including patients with sepsis, due to increased risk of mortality and renal replacement therapy (RRT).
- Do not use HES products, including 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection, in patients with severe liver disease.
- Do not use HES products, including 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection, in patients with known hypersensitivity to hydroxyethyl starch [see *General Warnings and Precautions (5.1)*]
- Do not use HES products in clinical conditions with volume overload.
- Do not use HES products in patients with pre-existing coagulation or bleeding disorders.
- Do not use HES products in patients with renal failure with oliguria or anuria not related to hypovolemia.
- Do not use HES products in patients receiving dialysis treatment.
- Do not use HES products in patients with severe hypernatremia or severe hyperchloremia.
- Do not use HES products in patients with intracranial bleeding.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylactoid Reactions

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)*]

5.2 Renal Dysfunction

Avoid use in patients with pre-existing renal dysfunction.

Discontinue use of 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection at the first sign of renal injury.

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

5.3 Coagulopathy

Monitor the coagulation status of patients undergoing open heart surgery in association with cardiopulmonary bypass as excess bleeding has been reported with HES solutions in this population. Discontinue use of 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection at the first sign of coagulopathy.

5.4 Fluid Equilibrium

Avoid fluid overload; adjust dosage in patients with cardiac or renal dysfunction. 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.

5.5 Monitoring: Laboratory Tests

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. Monitor liver function in patients receiving HES products, including 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection.

5.6 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

Serious adverse reactions reported in clinical trials include increased mortality and increased use of RRT in critically ill subjects including subjects with sepsis.

The most common adverse reactions after administration of 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection occurring in more than 1% of patients are: pruritus (itching; $\geq 1\%$ to $<10\%$), elevation of serum amylase ($\geq 1\%$ to $<10\%$; interference 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 ($\geq 1\%$ to $<10\%$).

Anaphylactoid reactions occur rarely in $<0.1\%$ after administration of hydroxyethyl starch solutions. Disturbances of blood coagulation beyond dilution effects can occur rarely in $<0.1\%$ depending on the dosage with the administration of hydroxyethyl starch solutions¹.

6.2 Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug or another patient population and 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 at different concentrations (2%, 4%, 6%, or 10%) and at cumulative doses of several mL up to 66 L². Of these 899 subjects, 602 were exposed to 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 a randomized controlled trial (RCT) of subjects (N=100) undergoing elective orthopedic surgery, 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection (N=49) or hetastarch (6% hydroxyethyl starch in 0.9% sodium chloride injection; N=51) were administered for intraoperative volume replacement.³ Mean infusion volumes were 1613 ± 778 mL for 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection group. Since calculated red blood cell loss 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, 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection vs. hetastarch, respectively) also must be viewed with caution.

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

Variable	Mean		Ratio 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection/Hetas tarch	
	6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection N=49	Hetas tarch N=51	Es timate	95% CI
Calculated red blood cell loss [L]*	1.17	1.31	0.910	[0.720; 1.141]
Factor VIII [%]*	100.5	81.4	1.244	[1.000; 1.563]
von Willebrand factor [%]*	97.7	88.7	1.128	[0.991; 1.285]
Fresh frozen plasma [mL]*	72	144	0.723	[0.000; 2.437]

* Exploratory analyses

A safety profile of 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection at least as favorable as for pentastarch was also demonstrated in studies where 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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.

Trials in critically ill adult subjects

Three RCTs followed critically ill adult subjects treated with different HES products for 90 days.

One trial using 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection in severe sepsis subjects (N=196) reported no difference in mortality (relative risk, 1.20; 95% CI, 0.83 to 1.74; p=0.33) and a trend for increased use of RRT (relative risk, 1.83; 95% CI, 0.93 to 3.59; p=0.06) in HES subjects⁴.

Another trial using 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection in a heterogeneous population of critically ill subjects admitted to the ICU (N=7000) reported no difference in mortality (relative risk, 1.06; 95% CI, 0.96 to 1.18; p=0.26) but increased use of RRT (relative risk, 1.21; 95% CI, 1.00 to 1.45; p=0.04) in HES subjects.⁵ A third trial in severe sepsis subjects (N=804) using an HES product not licensed in the U.S. (HES 130/0.42) reported increased mortality (relative risk, 1.17; 95% CI, 1.01 to 1.36; p=0.03) and increased use of RRT (relative risk, 1.35; 95% CI, 1.01 to 1.80; p=0.04) in HES subjects.⁶

6.3 Postmarketing Experience

Because adverse reactions are reported voluntarily post-approval from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to product exposure.

Among the very rarely occurring serious adverse drug reactions in patients treated with 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection, anaphylactic/anaphylactoid/hypersensitivity reactions or hypotension/shock/circulatory collapse were most frequently reported.

The following adverse reactions have been identified and reported during the post-approval use of different HES products in critically ill adult patients, including patients with sepsis:

- Mortality
- Renal: use of RRT

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. 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 embryo-lethal 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 *Animal Pharmacology and/or Toxicology (13.2)*]

Fertility studies on directly exposed animals have not been conducted.

There are no adequate and well-controlled studies in pregnant women. 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection (N=41) or 5% albumin (N=41). The mean dose of 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection administered was 16 ± 9 mL/kg.

In an additional trial, children from 2 - 12 years of age undergoing cardiac surgery were randomized to receive 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection (N=31) or 5% albumin (N=30). The mean dose administered was 36 ± 11 mL/kg.

Studies conducted in children have not been of sufficient size or follow-up duration to assess the risk

of renal injury and mortality in this patient population.

Dosage in children should be adapted to individual patient colloid needs, taking into account underlying disease, hemodynamics and hydration status.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection (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

6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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

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:

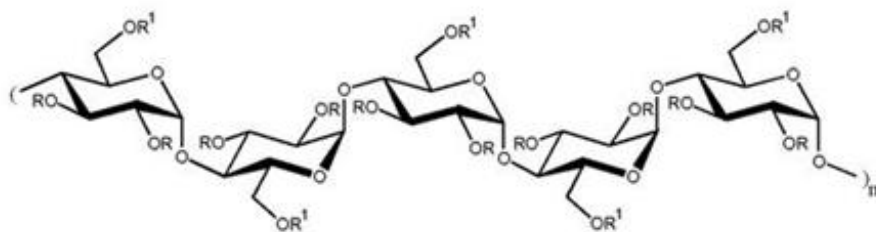
Hydroxyethyl Starch 130/0.4.....	6 g
Sodium Chloride USP.....	900 mg
Water for Injection USP.....	qs

In addition, as required sodium hydroxide may be 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 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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, -CH₂CH₂OH

R¹ = -H, -CH₂CH₂OH or glucose units

Not made with natural rubber latex, PVC or DEHP.

The plastic container is made from a multilayered film specifically developed for parenteral drugs. It contains no plasticizers and exhibits virtually no leachables. The solution contact layer is a rubberized copolymer of ethylene and propylene. The container is nontoxic and biologically inert. The container-solution unit is a closed system and is not dependent upon entry of external air during administration. The container is overwrapped to provide protection from the physical environment and to provide an additional moisture barrier when necessary.

The closure system has two ports; the one for the administration set has a tamper evident plastic protector and the other is a medication addition site. [see *Directions for Use of EXCEL® Container (2.3)*]

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 (C₂/C₆ 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 alpha-1-4-connected glucose units with several alpha-1-6-branches. Substitution of hydroxyethyl groups on the glucose units of the polymer reduces the normal degradation of amylopectin by alpha-amylase in the body. The low molar substitution (0.4) is the main pharmacological determinant for the beneficial effects of 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection on pharmacokinetics, intravascular volume and hemodilution⁸. To describe the molecular weight and molar substitution characteristics of the hydroxyethyl starch in 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection, the compound is designated as hydroxyethyl starch 130/0.4.

12.2 Pharmacodynamics

After isovolemic exchange of blood with 500 mL of 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 weight⁸. 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 alpha-amylase prior to excretion via the renal route.

The mean *in vivo* molecular weight of 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection to healthy volunteers, plasma levels of 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection remain at 75% of peak concentration at 30 minutes post-infusion and decrease to 14% at 6 hours post-infusion. Plasma levels of 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection return to baseline levels 24 hours following infusion. Plasma clearance, volume of

distribution, and elimination half-life of 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection in healthy volunteers following IV administration of 500 mL were 31.4 mL/min, 5.9 liters, and 12 hours, respectively. Approximately 62% of 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection was excreted as hydroxyethyl starch molecules in urine within 72 hours.

The pharmacokinetics of 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection was excreted as hydroxyethyl starch molecules in urine within 72 hours.

Renal Impairment:

Following a single intravenous administration of 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection (500 mL) in subjects with varying degrees of renal dysfunction, the AUC and clearance of 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection returned to baseline levels 24 hours following infusion. Approximately 59% and 51% of 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection were excreted as hydroxyethyl starch molecules in urine within 72 hours in subjects with creatinine clearance ≥ 30 mL/min and <30 mL/min, respectively⁹.

There are no data available on the use of 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 Pharmacology and/or Toxicology

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.

Pharmacology

The pharmacodynamic effect of 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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).

6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection and pentastarch solutions following induced hemorrhagic shock (67% and 50% blood loss). In the 67% induced bleeding group receiving 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection (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 ¹⁴C-hydroxyethyl starch 130/0.4 and 10% ¹⁴C-hydroxyethyl starch 200/0.5 solutions was carried out⁶. 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 ¹⁴C-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

6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 multicenter, double-blind RCT in subjects (N=100) undergoing elective orthopedic surgery was conducted in the U.S. to evaluate 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection (N=49) compared with hetastarch (6% hydroxyethyl starch in 0.9% sodium chloride injection) (N=51) for intraoperative volume replacement therapy³. 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 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection and 1584 ± 958.4 mL for hetastarch. The 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection/hetastarch ratio estimate of 1.024 with a 95% CI of 0.84 to 1.25 was within the equivalence range (0.55 to 1.82) prespecified in the study protocol. This indicated that 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 no difference was found between treatment arms for the first safety endpoint (calculated red blood cell loss), 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 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection 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 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection as compared to pentastarch resulting in a lower *in vivo* molecular weight and increased elimination from the circulation.

Trials in critically ill adult subjects

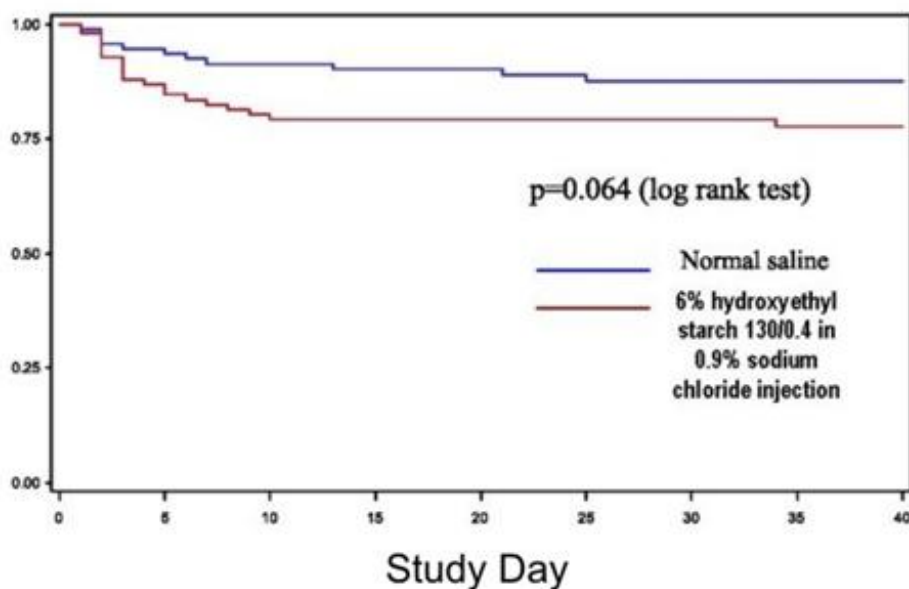
A multicenter, double-blind RCT of subjects (N=196) with severe sepsis ≥ 18 years old compared 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection (n=100) with 0.9% sodium chloride (n=96) infused over a maximum of 4 days for volume replacement therapy.⁴ The primary endpoint was volume of study drug (mL) required to achieve initial hemodynamic stabilization (HDS). HDS was based on prespecified criteria for MAP, CVP, urine output and central venous oxygen saturation. Acute renal failure was prospectively defined as use of RRT or doubling of baseline serum creatinine at some point during the 90-day observation period. Two scoring systems based on changes in serum creatinine concentration and urine output used to assess severity of acute kidney injury, AKIN (Stage 1, Stage 2, Stage 3) and RIFLE (Risk, Injury, Failure, Loss, End-stage kidney disease), also were evaluated.

In subjects achieving HDS (N=88 vs. 86), significantly less 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection was required to reach HDS compared with 0.9% sodium chloride: 1379 mL ± 886 (6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection) vs. 1709 ± 1164 mL (0.9% sodium chloride), representing a mean difference of 331 mL (95% CI, -640 mL to -21 mL, p=0.02). Less time was needed from start of study drug to achievement of HDS in the 6% hydroxyethyl starch

130/0.4 in 0.9% sodium chloride injection group compared with the 0.9% sodium chloride group (11.8 hours \pm 10.1 hours vs. 14.3 hours \pm 11.1 hours, mean \pm SD).

The number of treatment emergent serious adverse events (SAEs) (53 vs. 44) and the number of treatment emergent SAEs leading to death (38 vs. 32) in the 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection and normal saline treatment arms, respectively, during the 90-day observation period did not reach statistical significance. More 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection subjects than 0.9% sodium chloride subjects were treated with RRT: 21 (21%) vs. 11 (12%) (relative risk, 1.83; 95% CI, 0.95 to 3.58; $p=0.08$). Kaplan-Meier curves for time-to-RRT (Figure 1, below) showed a trend against 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection ($p=0.064$, log-rank test). The number of subjects meeting AKIN Stage 1, Stage 2, and Stage 3 criteria was 21 (21%) vs. 21 (22%), 5 (5%) vs. 6 (6%) and 22 (22%) vs. 17 (18%), 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection vs. 0.9% sodium chloride, respectively. Corresponding data for RIFLE stages Risk, Injury, and Failure were 13 (13%) vs. 11 (12%), 4 (4%) vs. 5 (5%), and 5 (%) vs. 7 (7%), respectively. [see *Adverse Reactions* (6)]

Figure 1: Kaplan-Meier Curves for time to RRT



Another multicenter, double-blind RCT in a heterogeneous adult ICU population (N=7000) that included subjects with sepsis as well as trauma subjects and postoperative elective surgery subjects, compared 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection with 0.9% sodium chloride for volume replacement therapy.⁵ The primary endpoint was death within 90 days. Secondary outcomes included incidence of acute kidney injury defined by RIFLE criteria, use of RRT, and new organ failure based on SOFA score. 90-day mortality was not different overall (597 (18%) 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection subjects vs. 566 (17%) 0.9% sodium chloride subjects; relative risk, 1.06; 95% CI, 0.96 to 1.18; $p=0.26$) or in six pre-defined subgroups including subjects with sepsis. Significantly more 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection subjects were treated with RRT: 235 (7.0%) vs. 196 (5.8%) (relative risk, 1.21; 95% CI, 1.00 to 1.45; $p=0.04$; $p=0.05$ when adjusted for covariates). In a post hoc analysis, use of 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection during the first seven days of therapy was associated with increased serum creatinine levels and decreased urine output; in a pre-planned analysis the number of subjects with RIFLE stages Risk and Injury was less frequent in the 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection vs. 0.9% sodium chloride group: 1788 (54.0%) vs. 1912 (57.3%; $p=0.007$) and 1130 (34.6%) vs. 1253 (38.0%; $p=0.005$), respectively. There was no statistical difference in RIFLE stage F: 336 (10.4%) vs. 301 (9.2%), 6% hydroxyethyl starch

130/0.4 in 0.9% sodium chloride injection vs. 0.9% sodium chloride, respectively. 6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection subjects experienced lower rates of new cardiovascular organ failure (hypotension) (36.5% vs. 39.9%; relative risk, 0.91; 95% CI, 0.84 to 0.99; p=0.03) but an increased SOFA score for hepatic function (bilirubinemia) (1.9% vs. 1.2%; relative risk, 1.56; 95% CI, 1.03 to 2.36; p=0.03). [see *Adverse Reactions in Clinical Trials (6.2)*]

A third multicenter, double-blind RCT performed in severe sepsis subjects (N=804) compared HES 130/0.42 in Ringer's acetate injection (RA), an HES solution not approved in the U.S. with modified RA for volume replacement therapy. The composite primary endpoint was mortality or dialysis-dependence up to 90 days after randomization. Secondary endpoints included death at 28 days, and acute kidney injury defined as use of RRT, a renal SOFA score ≥ 3 in subjects with renal SOFA ≤ 2 (serum creatinine < 2.0 mg/dL or urinary output < 171 mL per day) at randomization; doubling of serum creatinine. At the end of the 90 day study period, both mortality and use of RRT in the ITT population (N=798) were significantly higher in the HES 130/0.42 treatment arm: 201 (51%) vs. 172 (43%)(relative risk, 1.17; 95% CI, 1.01 to 1.36; p=0.03) and 87 (22%) vs. 65 (16%)(relative risk, 1.35; 95% CI, 1.01 to 1.80; p=0.04), respectively; one subject in each treatment cohort was dependent on dialysis on day 90. Mortality at 28 days was not different between groups (154 (39%) vs. 144 (36%); relative risk, 1.08; 95% CI, 0.90 to 1.28; p=0.43); use of RRT or renal SOFA score ≥ 3 , and doubling of serum creatinine, were numerically higher in the HES 130/0.42 cohort: 129 (32%) vs. 108 (27%)(relative risk, 1.20; 95% CI, 0.97 to 1.48; p=0.10) and 148 (41%) vs. 127 (35%)(relative risk, 1.18; 95% CI, 0.98 to 1.43; p=0.08), respectively. In a post hoc analysis, the number of subjects with RIFLE Risk, Injury, or Failure was 52 (14%) vs. 73 (20%), 62 (17%) vs. 53 (15%) and 84 (23) vs. 67 (18%), HES 130/0.42 vs. RA, respectively. [see *Adverse Reactions in Clinical Trials (6.2)*]

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride injection for intravenous infusion is supplied sterile and nonpyrogenic in EXCEL® Containers. The 500 mL containers are packaged 12 per case.

<u>NDC</u>	<u>REF</u>	<u>Volume</u>
0264-1968-10	L9681	500 mL

16.2 Storage

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

Storage in automated dispensing machines: Brief exposure up to 2 weeks to ultraviolet or fluorescent light does not adversely affect the product labeling legibility; prolonged exposure can cause fading of the red label. Rotate stock frequently.

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.

Rx only

EXCEL is a registered trademark of B. Braun Medical Inc.

B. Braun Medical Inc.

Irvine, CA 92614-5895 USA

1-800-227-2862

www.bbraun.com

Made in USA

Y36-002-767 LD-323-1

6% Hydroxyethyl Starch 130/0.4 in 0.9% Sodium Chloride Injection

Y94-003-142

LD-332-1

FOR INTRAVENOUS INFUSION ONLY

REF L9681

NDC 0264-1968-10

500 mL

EXCEL® CONTAINER

Each 100 mL contains:

Hydroxyethyl starch 130/0.4

6 g

Sodium chloride USP

900 mg

Water for Injection USP

qs

Electrolytes (mEq/L) Sodium 154, Chloride 154

Calculated osmolarity 308 mOsm/L

pH 4.0 to 5.5

May contain sodium hydroxide for pH adjustment.

If administered by pressure infusion, air should be withdrawn or expelled from the bag through the medication/administration port prior to infusion.

Sterile. Nonpyrogenic. Single dose container.
Use immediately after opening. Discard unused portion.
Use only if solution is clear and container is undamaged.
Usual dosage: See Package Insert.

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

Not made with natural rubber latex, PVC or DEHP.

Rx only

EXCEL is a registered trademark of B. Braun Medical Inc.

B. Braun Medical Inc.

Irvine, CA 92614-5895 USA

1-800-227-2862

www.bbraun.com

Made in USA

Do not remove overwrap until ready for use. After removing the overwrap, check for minute leaks by squeezing container firmly. If leaks are found, discard solution as sterility may be impaired.

Y94-003-140

LD-234-1

LOT

EXP

NDC BARCODE

EXP. LOT BARCODE

6% Hydroxyethyl Starch 130/0.4 in 0.9% Sodium Chloride Injection

Y94-003-142
LD-332-1

FOR INTRAVENOUS INFUSION ONLY

-0-

REF L9681

500 mL

-1-

NDC 0264-1968-10

EXCEL[®] CONTAINER

Each 100 mL contains:

Hydroxyethyl starch 130/0.4

6 g

Sodium chloride USP

900 mg

Water for Injection USP

qs

-2-

Electrolytes (mEq/L) Sodium 154, Chloride 154

Calculated osmolarity 308 mOsm/L

pH 4.0 to 5.5

-2-

May contain sodium hydroxide for pH adjustment.

If administered by pressure infusion, air should be withdrawn or expelled from the bag through the medication/administration port prior to infusion.

-3-

Sterile. Nonpyrogenic. Single dose container.

Use immediately after opening. Discard unused portion.

Use only if solution is clear and container is undamaged.

Usual dosage: See Package Insert.

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

-3-

Not made with natural rubber latex, PVC or DEHP.

Rx only



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-4-

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-4-

Do not remove overwrap until ready for use. After removing the overwrap, check for minute leaks by squeezing container firmly. If leaks are found, discard solution as sterility may be impaired.

LOT

EXP

HYDROXYETHYL STARCH IN SODIUM CHLORIDE

hydroxyethyl starch in sodium chloride injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0264-1968
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
HYDROXYETHYL STARCH 130/0.4 (UNII: 1GVO236S58) (HYDROXYETHYL STARCH 130/0.4 - UNII:1GVO236S58)	HYDROXYETHYL STARCH 130/0.4	6 g in 100 mL
SODIUM CHLORIDE (UNII: 451W47IQ8X) (SODIUM CATION - UNII:LYR4M0NH37, CHLORIDE ION - UNII:Q32ZN48698)	SODIUM CHLORIDE	900 mg in 100 mL

Inactive Ingredients

Ingredient Name	Strength
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0264-1968-10	12 in 1 CASE		
1		500 mL in 1 CONTAINER; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA110013	01/09/2015	

Labeler - B. Braun Medical Inc. (002397347)

Revised: 1/2015

B. Braun Medical Inc.