SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

VOLİZOLEN (HES 130/0.4) 6 % electrolyte solution for I.V. infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

Each 100 ml of solution:

-Hydroxyethyl starch (HES 130 / 0.4): 6 g (Average molecular weight 130.000; Substitution degree 0.38-0.45)

-Sodium chloride: 0.602 g

-Sodium acetate trihydrate: 0.463 g

- Potassium chloride: 0.03 g

- Magnesium chloride hexahydrate: 0.03 g

Osmolarity: 286.5 mOsm / l

pH: 5.7-6.5

Excipients:

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sterile- apyrogen solution for intravenous infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- In the prophylaxis and treatment of hypovolemia.
- In maintaining blood volume in surgical procedures.

4.2 Posology and method of administration

Posology/frequency and duration of administration

Infusion doses up to 33 ml / kg / day, the most commonly used dose in clinical trials, are used. Experiments are limited to 33 ml / kg / day and 50 ml / kg / day.

Maximum daily dose

The highest dose of VOLİZOLEN applicable for a 70 kg patient corresponds to 3500 ml of maximum 50 ml of VOLİZOLEN (equivalent to 3 g of hydroxyethyl starch, 6.85 mmol of sodium and 0.2 mmol of potassium per kilogram) per kilogram.

Application time: VOLİZOLEN can be applied repeatedly for a few days according to the needs of the patient. The course of treatment varies depending on the degree of the patient's hypovolemic and shock state, hemodynamic status and hemodilution.

Method of administration:
It is for intravenous use only.
Despite the possibility of anaphylactic reaction, the first 10-20 ml of the solution is applied slowly to the patient under close follow-up.

The daily dose and infusion rate may vary depending on the patient's blood loss, hemodynamics and hemodilution.
Additional information on special populations:

Renal/Hepatic failure:
Patients with renal and hepatic failure should not use (see section 4.3).

Pediatric population:
It is not recommended to use HES products in children since data in children is limited. (See section 4.4 and 5.1).

Geriatric population:
In a study on a product similar to VOLİZOLEN, no significant difference was found between patients over 65 years of age and young patients in terms of effect or safety. In other studies, there have been no reports of specific risks on the geriatric population.

4.3 Contraindications
VOLİZOLEN is contraindicated in the following cases:
- Persons known to be allergic to hydroxyethyl starch or corn,
- Intracranial or cerebral hemorrhages,
-Kidney disorders or kidney replacement therapy
- In case of hyperhydration, especially pulmonary edema and congestive heart failure,
- In cases of severe hypernatremia or severe hyperchloremia,
- Sepsis,
- With severe liver disease,
- In burns,
- Critical patients (usually in the intensive care unit),

- With pulmonary edema,
- In those with dehydration,
- In those with congestive heart failure,
- With severe coagulopathy,
- In patients who have undergone organ transplantation,

4.4 Special warnings and precautions for use

If a hypersensitivity reaction is observed, drug administration should be discontinued immediately and appropriate treatment should be administered until symptoms clear. Patients should be closely monitored against the risk of an allergic (anaphylactic / anaphylactoid) reaction and infusion should be started at a low rate.

In general, excessive fluid overload caused by overdose should be avoided. Caution should be exercised, especially in patients with cardiac disorders or severe renal dysfunction.

In case of severe dehydration, a crystalloid solution should be given first.

In critical patients, crystalloids should be used primarily, and VOLİZOLEN should only be used if the crystalloids are insufficient to stabilize patients and the expected benefit outweighs the risk.

Dose reduction in critical patients, the actual needs of the patient and the severity of the disease should be taken into consideration and the minimum effective dose should be given.

Special attention should be paid to patients with severe electrolyte disorders such as hyperkalaemia, hypernatremia, hypermagnesemia, hyperchloremia.

In cases where metabolic alkalosis and alkalization should be avoided clinically, salt based products similar to HES 130 / 0.4 in 0.9% sodium chloride solution should be preferred.

Surgery and trauma:

There is no strong long-term safety data in surgical patients and trauma patients. The expected benefit of treatment should be carefully weighed against this uncertainty associated with long-term safety. Other available treatments should be considered.

The volume replacement indication with HES should be carefully evaluated. Hemodynamic monitoring is required for volume and dose control.

It is important to administer appropriate fluid, monitor kidney function and fluid balance regularly. The application should be stopped at the first sign of kidney damage.

Excessive fluid loading should be avoided due to overdose or rapid infusion. The dose should be carefully adjusted, with special attention to patients with pulmonary and cardiovascular disorders

Serum electrolytes, fluid balance and kidney function should be closely monitored.

Caution should be exercised in patients with severe hepatic impairment and severe bleeding disorders (especially hemophilia and Von Willebrand disease). Possible Factor VIII measurement is recommended in order to monitor hemostasis regularly with APTT measurement and to determine Von Willebrand disease in the use of high dose or recurrent HES.

HES should be stopped at the first sign of coagulopathy.
It is not recommended to use products containing HES in the priming solution during open heart surgery associated with cardiopulmonary bypass, as this may cause excessive bleeding.

In general, significant dilution of blood can make it difficult to determine the blood group. To ensure that the blood group is determined correctly, blood samples must be taken before applying VOLİZOLEN in high volumes.

Temporarily increased serum alpha-amylase concentrations can be observed after administration of HES solutions. The increase in amylase is due to the formation of an enzyme substrate complex between the amylase and HEP and thus its slowing in elimination. Diagnosis of dysfunction of pancreatic functions should not be decided. (see Section 4.8).

High doses of HES solutions should not be used in the treatment of hypovolemic patients, as this may result in severe hemodilution.

The data in children are limited, so the use of HES products in this population is not recommended (see section 4.2).

Pruritus is a widespread complication, especially due to extended and high-dose use of hydroxyethyl starch. HES-induced pruritus may be delayed 1-6 weeks after application, and this effect may have gained serious and long-term resistance. Usually it does not respond to treatment. However, pruritus seen after application may be at a lower incidence due to the low molecular weight of HEPP 130/4.4, its low grade of sub-substrate, its small amount of storage in the tissues, and the intra-vascular resistance associated with its short half-life.

Products containing HES are contraindicated in the treatment of kidney disorders or kidney replacement (see section 4.3). When the first sign indicating kidney damage is detected, the use of HES should be terminated. Renal replacement therapy has been reported within 90 days of HES application. Therefore, follow-up of renal function of all patients should be continued for at least 90 days.
This medicinal product contains 6.02 g (103 mmoL) of sodium per 1000 ml. This should be considered for patients on a controlled sodium diet. For anaphylactic reactions, see section 4.8.

4.5 Interaction with other medicinal products and other forms of interaction
The use of concomitant HES medicinal products in patients treated with heparin anticoagulant NSAIDs and sodium valproate may increase clotting time.

VOLİZOLEN should not be mixed with other drugs due to the risk of microbial contamination and incompatibility. If any drug supplement is specified, it is important to pay attention to the general compatibility specific to that drug. Precipitation may occur if VOLİZOLEN is mixed especially with solutions containing phosphate and carbonate.

Care should be taken when applying with sodium and potassium retention products.

During administration of hydroxyethyl starch, serum amylase levels may increase, preventing the diagnosis of pancreatitis (See Sections 4.4 and 4.8).

4.6 Pregnancy and lactation

General recommendation
Pregnancy category: C

Women with childbearing potential/Contraception
There is not enough information. No studies on the use of VOLİZOLEN in women of childbearing potential have been performed

Pregnancy

There are no clinical data on the use of VOLİZOLEN in pregnant women.
Limited clinical trial data are available on the use of a single dose of VOLİZOLEN in pregnant women entering cesarean delivery with spinal anesthesia.
It has not been determined that VOLİZOLEN has a negative effect on patient safety; There was also no negative effect on the newborn (see section 5.1).
Animal reproductive toxicology studies have not been conducted, but animals have had vaginal bleeding, embryotoxic and teratogenic effects after repeated administration of similar products. (see Section 5.3).
VOLİZOLEN should not be used during pregnancy unless necessary.

Lactation
It is not known whether hydroxyethyl starch passes into milk. Many drugs pass into breast milk, so care should be taken when applying VOLİZOLEN to breastfeeding people.
There is no study on this subject on animals.
Whether to continue breastfeeding or drug use should be decided by considering the mother's need for VOLİZOLEN treatment and the benefit of breastfeeding to the baby.

Reproductive ability / Fertility
There is not enough information.

4.7 Effects on ability to drive and use machines
This section is not valid due to its intended use and method of application.

4.8 Undesirable effects
The undesirable effects are defined as follows: Very common (>1/10), common (>1/100 to <1/10), uncommon (>1/1,000 to <1/100), rare (>1/10,000 to <1/1,000), very rare (<1/10,000), frequency Unknown (cannot be estimated from the available data)

Blood and lymphatic system disorders

Very common: decrease in plasma protein concentrations and hemotocrit due to hemodilution

Common: High doses of hydroxyethyl starch cause dilution of clotting factors, which can affect blood clotting. After administration of high doses, bleeding time and aPTT may increase and the FVIII / vWF complex concentration may decrease (see section 4.4).

Rare: Coagulation disorders due to the administered dose of hydroxyethyl starch.

Immune system disorders

Rare: Anaphylactic reactions (Hypersensitivity, influenza-like symptoms, bradycardia, tachycardia, bronchospasm, non-cardiac pulmonary edema). In the case of an intolerance reaction, the infusion should be discontinued immediately and appropriate treatment, if necessary.

Hepatobiliary diseases
Unknown: hepatic injury

Skin and subcutaneous tissue disorders
Common: Itching (Usually dose dependent and seen during long treatment. Itching may continue after discontinuation of treatment.)

Kidney and urinary diseases
Unknown: renal damage

Investigations
Very common: Increased serum amylase levels (Can be confused with pancreatitis. High amylase level causes the formation of enzyme substrate complex of hydroxyethyl starch with amylase, pancreatitis status should not be considered.). Temporary elongation during bleeding and clotting times; dilution of plasma proteins, drop in hematocrit (when applied in high volumes)

4.9 Overdose and therapy

Overdose can cause overload in the circulatory system (eg pulmonary edema). In this case, the infusion should be stopped immediately and, if necessary, a diuretic drug should be administered to the patient.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Blood substitutes and plasma protein fractions, starch solutions
ATC Code: B05AA07

VOLİZOLEN is an intravascular volume expander and hemodilution providing artificial colloid.Its effect depends on the substitution (0.4) of the hydroxyethyl group, molecular weight (130,000 Da), concentration (6%), dose and infusion rate. The hydroxyethyl starch (130 / 0.4) contained in VOLİZOLEN is a kind of waxy starch derivative and its substitution structure (C2 / C6 ratio) is an estimated 9: 1.

In studies carried out on similar products of 500 ml containing HES 130 / 0.4 (6%) in 0.9% sodium chloride solution, plateau-like unexpanded volume increase in 30 minutes reaches an estimated 100% and takes 4-6 hours.

Blood isovolemic exchange with HES 130 / 0.4 in 0.9% sodium chloride solution maintains blood volume for at least 6 hours.

VOLİZOLEN is an isotonic solution containing sodium (Na^+), potassium (K^+), magnesium (Mg^{++}), chloride (Cl^-) and acetate (CH_3COO^-) electrolytes. Acetate is an anion that is oxidized by various organs and has an alkalizing feature.

VOLİZOLEN contains low amounts of chloride, so it does not produce hyperchloremic metabolic acidosis, especially at doses where high-dose infusion is required or when there is a risk of developing metabolic acidosis in the patient.

In cardiac surgery, chloride levels drop significantly and the base excess level shows less negative for VOLİZOLEN.

Treatment of pregnant women who will have cesarean delivery

There are limited clinical data on the use of a single dose of VOLİZOLEN in pregnant women who will have cesarean delivery with spinal anesthesia. The occurrence of hypotension is significantly lower for VOLİZOLEN compared to crystalloid (36.6% vs. 55.3%). Overall, the efficacy assessment shows that VOLİZOLEN has significant benefits in preventing hypotension and severe hypotension compared to crystalloid control.

Treatment in children:

There are no clinical studies in children. However, there are similar studies on products containing HES 130 / 0.4 (6%) in 0.9% sodium chloride solution. In the study, which included a group of 41 people consisting of newborns and infants (<2 years old), a drug of 16 ± 9 ml / kg administered in non-cardiac surgery was found safe and tolerated by hemodynamic stabilization.

If VOLİZOLEN is to be used in children, the dose should be individualized, taking into account the underlying disease and hemodynamic status. Pharmacokinetic data for children are not available.

5.2 Pharmacokinetic properties

The pharmacokinetics of hydroxyethyl starch are mixed and vary depending on the molecular weight, the degree of molar substitution, the structure of the substitution (C2 / C6 ratio).
Absorbation:
No data are available.

Distribution:
The volume of distribution is around 5.9 liters. The plasma level of HES 130 / 0.4 (6%) is 75% of the maximum dose 30 minutes after application. After 6 hours, the plasma level drops to 14%. Plasma level returns to baseline within 24 hours after 500 ml single dose of hydroxyethyl starch.

Biotransformation:
Molecules larger than 60.000-70.000 Da are metabolised by plasma α-amylase.

Elimination:
Those with a molecular weight of hydroxyethyl starch applied below 60.000-70.000 Da are excreted in the urine. Larger molecules are excreted renally after being metabolized by plasma α amylase.
When 500 ml HES 130 / 0.4 (6%) was applied, plasma clearance was 31.4 ml / min. AUC is 14.3 mg / ml x s and a nonlinear pharmacokinetic has been observed. The result of a single application approximately 62% of the amount applied in 72 hours was discarded. Plasma half-life $t_{1/2\alpha}$ = 1.4 s and $t_{1/2ß}$ = 12.1 s.

AUC increased when the same dose (500 ml) was administered to the patient with mild stable-severe kidney damage. The last half-life and HES peak concentration were not affected by renal damage. Plasma levels returned to normal within 24 hours of infusion. Creatinine clearance> 50 ml / min when administered at the same dose (500 ml) to patients with mild to severe renal impairment. AUC value is increased 1.7 times in patients with <50 ml / min (95% confidence interval 1.44 and 2.07). Terminal half-life and peak HES concentrations are not affected by kidney failure. When $Cl_{Cr} \geq 30$ ml / min, 59% of the drug was excreted in the urine. When Cl_{Cr} is 15-30 ml / min, this figure decreased to 51%.
There is no information regarding the use of VOLİZOLEN in dialysis.

Linearity/Non-linearity:
There is no data available.

In another pharmacokinetic study; Eight stable patients who were in the final stage of kidney disease (ESRD) received a single dose of 250 ml (15 g) HEP 130 / 0.4 (6%). 3.6 g (24%) of the HES dose was eliminated during the 2 hour hemodialysis session. The average HES plasma concentration after 24 hours is 0.7 mg / ml. The average plasma concentration of the HES after 96 hours is 0.25 mg / ml. HES 130 / 0.4 (6%) is contraindicated in patients receiving dialysis therapy (See section 4.3).

5.3 Preclinical safety data
Subchronic toxicity

As a result of intravenous infusion of 9 g hydroxyethyl starch, no signs of toxicity were observed in rats and dogs for 3 months except for increased workload in kidney and liver.

The lowest toxic dose for VOLİZOLEN containing hydroxyethyl starch is 9 g / kg v.a / day. This is about 3 times the therapeutic dose used for human.

In rats and dogs, intravenous infusion of 9g of hydroxyethyl starch present in VOLİZOLEN kg / v.a. / day, increased work of kidneys and liver, hydroxyethyl in reticulo-endothelial system ,starch reuptake and metabolism did not result in signs of toxicity except hepatic parenchyma and other tissues related to the non-physiological status of animals during the test.

Reproductive toxicity

Hydroxyethyl starch in VOLİZOLEN has no teratogenic effect on rats and rabbits. The dose showing embryo lethal effect was found as 5 g / kg bw / day in rabbits. In pregnant and lactating rats, baby's body weight decreased and developmental retardation was observed as a result of bolus injection of this dose. However, embro-flutotoxicity in rats and rabbits was observed at maternal toxic doses. The effects of fluid loading are observed in mother animals. Fertility studies have not been conducted on directly exposed animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Water for injection

Sodium hydroxide / Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities
In general, it is recommended not to mix other drugs into VOLİZOLEN solution.

6.3 Shelf Life

24 months

6.4 Special precautions for storage
Store at room temperature below 25°C.Do not freeze it.

6.5 Nature and contents of container
VOLİZOLEN (HES 130/0.4) 6 % electrolyte solution for I.V. infusion product is offered for sale in 500 ml PP bags.

6.6 Special precautions for disposal and other handling

It is single use only.
It should be used immediately after opening the bag. The product in which an unusual situation is observed should not be used. The coating material on the bag must be removed before use. Unused products or waste materials must be disposed of in accordance with the "Medical Waste Control Regulation" and "Regulation on Control of Packaging and Packaging Waste".

Solution and expiration date should be checked before use.
Application is done intravenously with sterile pyrogen sets.

Only products that are clear, particle-free and intact in packaging integrity should be used.

The administration should be started as soon as possible after the application set is attached to the product.

In order to prevent an air embolisation that may occur due to the residual air in the bag, no serial connection should be made with other infusion fluids.

The solution should be applied using the aseptic technique through the sterile application set. In order to prevent air from entering the system, liquid must be passed through the application set before use.

Additional medication may be added before and during infusion with the aid of Injection a needle in aseptic conditions. The final product's isotonicity should be determined before parenteral administration.

The added drug must be completely mixed with the solution before application to the patient. Solvents containing additional drug should be used immediately after drug addition; it should not be stored for later use.

Addition of additive or wrong application technique may result in a fever reaction due to pyrogen contamination of the product. If an adverse reaction occurs, the infusion should be terminated immediately.

Do not store partly used solutions
Do not reconnect partly used bags to the administration systems.

To open:
1. Check the integrity of the outer packaging and check for leaks; Do not use if the packaging is damaged.
2. Tear off the protective outer packaging.
3. Check for robustness by squeezing the inner bag firmly. Check the clarity of the solution in the bag and that is free of foreign substances.

Preparation for administration:
1. Hang the bag.
2. Remove the protective cover from the application port.
3. Stick the spike of the application set firmly in the application tip.
4. The instructions for use of the set must be followed for the administration of the solution.

Addition of additional drug:
Attention: As with all parenteral solutions, all substances to be added to the product must be compatible with the product. If an addition is to be made, compatibility should be checked in the final mixture before administration to the patient.

Adding medication before administration
1. Disinfect the drug applicator.
2. Inject the drug to be added using syringe with 19 to 22 gauge needle.
3. Mix the solution and the added drug thoroughly. For high density medication such as potassium chloride, tap gently to the ports of the bag, while ports are upright to allow mixing.
Attention: Do not store bags mixed with additional medication.

Adding medication during administration
1. Close the clamp.
2. Disinfect the drug applicator.
3. Inject the drug to be added using syringe with 19 to 22 gauge needle.
4. Remove the solution from the hanger and invert.
5. In this position, tap gently both ports to allow mixing of solution and medication.
6. Return bag to its former position and open the clamp and continue administration.

7. MARKETING AUTHORISATION HOLDER

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