SUMMARY OF PRODUCT CHARACTERISTICS

Contraindications
Should not be used in patients with sepsis, renal failure or in critical conditions.
Please see Section 4.3.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT
VOLUHES (HES 130/0.4) 6% Solution for I.V. Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Drug substance:
1000 ml contains:
Poly (O-2-hydroxyethyl) starch 60.00 g
(Corn based molar substitution 0.38 - 0.45)
(Mean molecular weight: 130,000)
Sodium chloride……9.00 g
Na^+ 154 mmol
Cl^- 154 mmol

Theoretical osmolarity……..308 mOsmol/l
pH…….4.0 - 5.5

Excipients:
For excipients see section 6.1

3. PHARMACEUTICAL FORM
Solution for infusion.
VOLUHES is a clear to slightly opalescent, colorless to slightly yellow solution.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
It is indicated for the treatment of hypovolemia caused by acute blood loss, where crystalloid alone is not sufficient (see Sections 4.2, 4.3 and 4.4).

4.2 Posology and method of administration
Posology / frequency and duration of application:
Hydroxyethyl starch (HES) administration has to be limited in the initial phase of volume resuscitation with a time interval of maximum 24 hours.

The infusion of the first 10-20 ml has to be slow and the patient should be carefully monitored so that any anaphylactic/anaphylactoid reaction can be detected as soon as possible.

The daily infusion dose and rate depend on the patient's blood loss, the maintenance or restoration of hemodynamics, and the hemodilution (dilution effect).

The maximum daily dose for %6 HES (130/0.40) and %6 HES (130/0.42) is 30 ml/kg. Maximum daily dose should be calculated for other HES products.

The lowest effective dose should be administered. Continuous hemodynamic monitoring should be continued to stop infusion as soon as the appropriate hemodynamic targets are reached. The maximum recommended daily dose should not be exceeded.

Administration method:
Administered intravenously as infusion.

Special populations
Pediatric population:
Data are limited in children, so it is recommended not to use HES products in this population.

4.3 Contraindications

- Excessive sensitivity to the active substances or to any of the other excipients listed in Section 6.1.
- Sepsis
- Burns
- Renal failure or renal replacement therapy
- Intracranial or cerebral hemorrhage
- Critical patients (typically those admitted to the intensive care unit)
- Hyperhydration

Pulmonary edema

- Dehydration
- Severe hypernatremia or severe hyperchloremia
- Severe hepatic dysfunction
- Congestive heart failure
- Severe clotting disorder
- Organ transplant patients

4.4 Special warnings and precautions for use

The patient should be closely monitored for the risk of allergic (anaphylactic/anaphylactoid) reactions and infusion should be performed at a low rate (see section 4.8).

Surgery and trauma:
There is a lack of robust, long-term safety data for patients who have undergone surgery and for traumatized patients. The expected benefit of treatment should be carefully weighed against this long-term safety-related uncertainty. Other appropriate treatment options should be considered.

The indication for volume completion with HES should be carefully considered and hemodynamic monitoring is required for volume and dose control (see also section 4.2).
Always excessive volume administration must be avoided due to overdose or too fast infusion. The dosage should be carefully adjusted in patients with pulmonary and cardiovascular problems. Serum electrolytes, fluid balance and renal function should be closely monitored.
HES products are contraindicated in patients with renal failure or renal replacement therapy (see section 4.3). The use of HES should be terminated at the first sign of renal damage.
The need for renal replacement therapy, which increased up to 90 days after HES application, was recorded. It is recommended to monitor renal function for at least 90 days.
Special care should be taken when treating patients with hepatic dysfunction and patients with blood clotting disorders.
In the treatment of hypovolemic patients, serious hemodilution caused by high doses of HES solutions should also be avoided. Blood clotting parameters should be carefully monitored in case of repeated applications. The use of HES should be discontinued in case of the first coagulation disorder.
The administration of HES products is not recommended for patients who will undergo open heart surgery with a cardiopulmonary bypass.

4.5 Interaction with other medicinal products and other forms of interaction
No interactions with other drugs are known to date.

Please refer to section 4.8 “Undesirable effects” concerning the concentration of serum amylase which can rise during administration of hydroxyethyl starch and can interfere with the diagnosis of pancreatitis.

4.6 Pregnancy and lactation
General recommendations
Pregnancy category: D

Women of childbearing potential /Contraception
For VOLUHES no clinical data on women of childbearing potential are available.

Pregnancy
For VOLUHES no clinical data on exposed pregnancies are available.
There are limited clinical study data available from the use of a single dose of VOLUHES in pregnant women undergoing Caesarean section with spinal anesthesia. No negative influence

of VOLUHES on patient safety could be detected; a negative influence on the neonate could also not be detected (see section 5.1).
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition or postnatal development (see section 5.3). No evidence of teratogenicity was seen. VOLUHES should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is unknown whether hydroxyethyl starch is excreted in human breast milk. The excretion of hydroxyethyl starch in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with VOLUHES should be made taking into account the benefit of breast-feeding to the child and the benefit of VOLUHES therapy to the woman.

VOLUHES should be used during early pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation
It is not known whether the hydroxyethyl starch passes into human milk. The passage of hydroxyethyl starch to milk was not studied in animals. A decision on whether to continue or not to breastfeed or to continue treatment with VOLUHES should be given considering the benefit of breastfeeding to the child and the benefit of VOLUHES to a nursing woman.
There are currently no clinical data available on the use of HES 130/0.4 (6%) in nursing women.

Fertility
Sufficient data are not available.

4.7 Effects on ability to drive and use machines
It is unknown on ability to drive and use machines.

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), and unknown (available data do not allow deciding)

Blood and lymphatic system disorders
Rare: Coagulation disorders

Immune system disorders
Rare: Medical products containing hydroxyethyl starch may cause anaphylactic/anaphylactoid reactions (hypersensitivity, mild flu-like symptoms, bradycardia, tachycardia, bronchospasm, non-cardiac pulmonary edema). In the event of an intolerance reaction, the infusion should be discontinued immediately and appropriate emergency medical treatment should be initiated.

Skin and subcutaneous tissue disorders
Common (dose dependent): Prolonged doses of hydroxyethyl starch at high doses may cause pruritus (pruritus), a known undesirable effect of hydroxyethyl starch.

Hepatobiliary diseases
Unknown (cannot be estimated from the available data): hepatic damage.

Kidney and urinary diseases
Unknown (cannot be estimated based on available data): Renal damage.

Investigations
Common (dose dependent): Serum amylase levels may increase during the application of hydroxyethyl starch and may be confused with pancreatitis. Increased amylase is caused by the formation of the enzyme-substrate complex of amylase and hydro-ethyl starch exposed to slow elimination and should not be seen as a diagnosis of pancreatitis.

Common (dose dependent): Dilution effects at high doses may result in a reduction in hematocrit and corresponding dilution of blood components such as coagulation factors and other plasma proteins.

4.9 Overdose
As with all volume complements, overdose can lead to overload of the circulatory system (eg, pulmonary edema). In such cases, the infusion should be stopped immediately and given a diuretic if necessary.

5. PHARMACOLOGIC PARTICULARS

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Plasma substitutes and plasma protein fractions
ATC code: B05AA07

VOLUHES is an artificial colloid for volume replacement whose effect on intravascular volume expansion and haemodilution depends on the molar substitution by hydroxyethyl groups (0.4), the mean molecular weight (130.000 Da), the concentration (6%) as well as the dosage and infusion rate.

Hydroxyethyl starch (130/0.4) contained in VOLUHES 10% is derived from waxy maize starch and has a substitution pattern (C2/C6 ratio) of approximately 9:1.

Infusion of 500 ml VOLUHES in 30 minutes in volunteers results in a plateaulike non-expansive volume increase of approximately 100% of the infused volume which lasts for approximately 4 to 6 hours.

Isovolaemic exchange of blood with VOLUHES maintains blood volume for at least 6 hours.
Treatment of pregnant women undergoing Caesarian section
There are limited clinical study data available from the use of a single dose of HES 130/0.4 (6%) in 0.9% sodium chloride in pregnant women undergoing Caesarean section with spinal anesthesia. The occurrence of hypotension was significantly lower for HES 130/0.4 (6%) compared to crystalloid control (36.6% vs. 55.3%). Overall efficacy evaluation showed significant benefits for HES 130/0.4 (6%) in the prevention of hypotension and in the occurrence of severe hypotension compared to crystalloid control.

5.2 Pharmacokinetic properties
The pharmacokinetics of hydroxyethyl starch is complex and depends on the molecular weight and mainly on the molar substitution degree.

Absorption:
No data

Distribution:
The mean in vivo molecular weight of VOLUHES in the plasma is 70,000 – 80,000 Da immediately after infusion and remains above the renal threshold throughout the therapeutic period.

The volume of distribution is about 5.9 liters. Within 30 minutes of infusion the plasma level of VOLUHES is still 75% of the maximum concentration. After 6 hours the plasma level has decreased to 14%. Following a single dose of 500 ml hydroxyethyl starch plasma levels almost return to baseline after 24 hours.

No significant plasma accumulation occurred even after a daily administration of 500 ml of a 10% solution to volunteers containing HES 130/0.4 over a period of 10 days. In an experimental model in rats using repetitive doses of 0.7g/kg BW per day of VOLUHES over 18 days, 52 days after the last administration tissue storage was 0.6% of the total administered dose.

Biotransformation:
When applied intravenously, molecules smaller than the renal threshold (60,000-70,000 Da) are readily excreted in the urine while larger ones are metabolized by plasma α-amylase.

Elimination:
When applied intravenously, molecules smaller than the renal threshold (60,000-70,000 Da) are readily excreted in the urine while larger ones are metabolized by plasma α-amylase before the degradation products are renally excreted.

Plasma clearance was 31.4 ml/min when 500 ml of HES 130/0,4 (%6) was administered, with an AUC of 14.3 mg/ml.h, which shows a non-linear pharmacokinetic. Plasma half-lives were t1/2α = 1.4 h and t 1/2ß = 12.1 h when 500 ml were administered on a single occasion.

Using the same dose [500 ml] in subjects with stable mild to severe renal impairment, the AUC moderately increased by a factor of 1.7 (95% confidence limits 1.44 and 2.07) in subjects with ClCr < 50 ml/min compared to > 50 ml/min. Terminal half-life and peak HES concentration were not affected by renal impairment. At ClCr ≥30 ml/min, 59% of the drug could be retrieved in the urine, vs 51% at ClCr 15 to 30 ml/min.

Linearity/ nonlinear conditions:
No data available.

In another pharmacokinetic study; eight stable patients who were in the final stage of kidney disease received a single dose of 250 mL (15 g) HES 130/0.4 (6%). 3.6 g (24%) of the HES dose was eliminated during a 2-hour hemodialysis session (500 ml dialysate per minute, Filter HD Highflux FX 50). 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%); It is contraindicated in patients receiving dialysis therapy (see section 4.3).

5.3 Preclinical safety data
Subchronic toxicity:
HES 130/0.4 in rats and dogs for 3 months, except for increased workload in the kidneys and liver, hydroxyethyl starch removal and metabolism in the reticulo-endothelial system, and a toxicity caused by hepatic parenchyma and other tissues associated with the non-physiological state of the animals during the test period. Intravenous infusion of 9 g hydroxyethyl starch contained in 6%/kg body weight/day did not result in any signs of toxicity.
The lowest toxic dose is greater than the hydroxyethyl starch in VOLUHES at 9 g/kg body weight/day, which is at least 5 times greater than the maximum human therapeutic dose levels.

Reproductive Toxicity:
Hydroxyethyl starch type present in HES 130/0.4 (6%) has no teratogenic properties in rats and rabbits.
Embryolethal effects were observed in rabbits at 50 ml/kg body weight/day. Bolus injection of this dose during pregnancy and breastfeeding in rats lowered the body weight of the offspring and caused developmental delays. Symptoms of excessive fluid overload were seen in mothers.
Fertility studies have not been conducted on directly exposed animals.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium hydroxide

Hydrochloric acid
Water for injections

6.2 Incompatibilities
The mixing with other drugs should be avoided. If, in exceptional cases, a mixture with other drugs is required, care should be taken with the compatibility (clouding or precipitation), hygienic injection and a good admixture.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store at temperature below 25°C, keep from light, do not freeze.

6.5 Nature and contents of packaging
In the box, 4 side is sealed with heat, PP bag with two outlets on each side, 500 ml (with and without sets).

6.6 Destruction of the residual materials human medicinal product and other special precautions
To be used immediately after the bottle or bag is opened.
Do not use VOLUHES after expiry date.
Any unused solution should be discarded.
Use only clear solutions and undamaged containers.
Keep out of reach of children

7. MARKETING AUTHORIZATION HOLDER
POLİFARMA İLAÇ SAN. VE TİC. A.Ş.
Vakıflar OSB Mah. Sanayi Cad. No: 22/1
Ergene/Tekirdağ/TURKEY

8. MARKETING AUTHORISATION NUMBER
2014/463

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13/12/2019