Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

HESAT 6% Solution for Infusion

2. Qualitative and quantitative composition

Each 1 ml of HESAT 6% Solution for Infusion contains:
Poly (O-2-hydroxyethyl) starch 60 mg
-Molar substitution: 0.36-0.45,
-Mean molecular weight: 130,000 Daltons
Sodium Chloride 0.9%

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Sterile solution for intravenous infusion.
A clear to slightly opalescent solution, colourless to slightly yellow solution.
pH 4.0-5.5

4. Clinical particulars

4.1. Therapeutic indications

It is indicated for the treatment of hypovolemia caused by acute blood loss where crystalloids alone are not sufficient (See Sections 4.2, 4.3 and 4.4).

4.2. Posology and method of administration

Posology/frequency and duration of administration

The use of hydroxyethyl starch (HES) should be limited during the initial phase of volume resuscitation with a maximum time span of 24 hours.

Hypovolemia and shock cases

Daily dose: The average daily administration dose is 250–1000 mL.

The infusion of the first 10-20 mL should be done slowly and the patient should be carefully monitored so that any anaphylactoid reaction can be detected as soon as possible.
The maximum daily dose is 30 ml / kg for 6% HES (130 / 0.40) and 6%

HES (130 / 0.42). The maximum daily dose should be recalculated for other HES products.
Maximum daily dose: 2 g HES / kg body weight = 33 mL / kg body weight (2500 mL for a 75 kg patient)
The lowest possible effective dose should be administered. As soon as hemodynamic targets suitable for treatment are reached, continuous hemodynamic monitoring should be continued to stop the infusion.
The maximum recommended daily dose should not be exceeded.

Infusion rate: If there is no special case, more than 500 ml HESAT 6%should not be given in 30 minutes.
Maximum infusion rate: 1.2 g / kg / hour HES = 20 mL / kg / hour (1500 mL / hour for a 75 kg patient)
Duration of administration: The duration of administration of HESAT 6%depends on the severity and duration of hypovolemia. Clinically and pharmacologically repeated uses are not disadvantageous.

Therapeutic hemodilution

The purpose of therapeutic hemodilution is to reduce the hematocrit to around 35-40%. Hemodilution can be isovolemic or hypervolemic.
Daily dose: 250 mL, 500 mL or 2x500 mL / day, depending on the needs of the patient.

Infusion rate:

250 mL in 0.5-2 hours

500 mL in 4-6 hours 2x500 mL in 8-24 hours
Duration of application: A therapeutic hemodilution treatment period with HESAT 6%should last no more than 10 days. Plasma protein levels, hematocrit and hemoglobin levels should be reassessed to prolong or repeat the treatment.
In the treatment of autonological disorders such as sudden hearing loss due to severe noise, tinnitus, the maximum daily dose is 500 mL and administered at a rate of 500 mL / 4-6 hours. Care should be taken not to drop the hemoglobin value below 10%.
Pediatric population:

Data in children is limited. For this reason, it is recommended that HES products should not be used in this population.

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 is determined by the patient's clinical condition, blood loss and hemoconcentration.

In young patients without cardiovascular and pulmonary risks, hemotocrit should not fall below 30% during the use of colloidal solutions.

The risk of loading colloidal solutions into the circulatory system should be taken into account as a result of applying fast or very high volumes.

Additional information on special populations:

Renal failure:
HESAT 6%should not be used in patients with renal insufficiency.

Hepatic failure:
There is no specific dosage recommendation for this group of patients, as there is no specific study for this population. However, patients with chronic hepatic disease should be especially observed, as it is contraindicated in conditions that may result from liver dysfunction, such as afibrinogenemia.

Pediatric population:
The efficacy and safety of HESAT 6%in children is unknown.

Geriatric population:
The dose and infusion rate to be applied are adjusted by the physician according to the current clinical condition of the patient.

During the leukapheresis process (continuous flow centrifuge), 250-700 mL venous is applied to the whole blood at constant 1: 8-1: 13 ratios.

4.3. Contraindications

HESAT 6%is contraindicated in the following cases:
- Hypersensitivity to active substances or any of the other excipients listed in Section 6.1
-Sepsis
- Burns
-Kidney failure or renal replacement therapy
-Intracranial or cerebral hemorrhage
-Patients in critical condition (typically admitted to the intensive care unit)
-Hyperhydration
-Pulmonary edema
- Dehydration
-Severe coagulation disorder
- Organ transplant patients
-Severe hepatic dysfunction
-People known to be allergic to hydroxyethyl starch or corn
-Severe hypervolemia and severe hyperhydration states
-Severe congestive heart failure and decompensated heart failure

-Kidney failure with oliguria or anuria or when serum creatinine is above 2 mg / dL
-Dialysis patients (since HES molecules are filtered through glomeruli)

4.4. Special warnings and precautions for use

Due to the risk of allergic (anaphylactoid) reactions, the patient should be closely monitored and the infusion should be performed at low speed (see section 4.8).

Surgery and trauma:
Robust long-term safety data are lacking for patients undergoing surgery and trauma. The expected benefit of treatment should be carefully weighed against this long-term safety-related uncertainty. Other suitable treatment options should be considered.

Indication of volume completion with HES should be carefully considered and hemodynamic monitoring is required for volume and dose control (see also Section 4.2).

Overloading should always be avoided due to overdose or very rapid infusion.
The dosage should be carefully adjusted, especially 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 impairment or in renal replacement therapy (see section 4.3). The use of HES should be stopped at the first sign of renal damage. An increase in the need for renal replacement therapy has been reported up to 90 days after HES application. It is recommended to monitor renal function in patients 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, severe hemodilution caused by high-dose HES solutions should also be avoided.

In the case of repeated applications, blood clotting parameters should be carefully monitored.
In the first sign of coagulation disorder, HES should be stopped. The use of HES products is not recommended due to the risk of excessive bleeding in patients undergoing open heart surgery due to cardiopulmonary bypass.

Patients should be monitored for fluid and electrolyte balance during HESAT 6% application.

In cases of shock due to fluid and electrolyte loss (severe vomiting, burns

and insufficiency), initial treatment with HESAT 6%should be followed by correction of fluid and electrolyte balance.

Serum creatinine level should be checked at the start of treatment. In cases where serum creatinine level is above 2 mg / dl, HESAT 6%should not be applied.

Hemodilution therapy should be applied carefully, especially in geriatric patients with borderline creatinine values (1.2 - 2 mg / dL). If absolutely necessary, serum creatinine levels should be monitored.

Although the creatinine values are normal, pathological urine findings may indicate that kidney damage is compensated. In such cases, serum creatinine should be checked daily.

In patients with normal serum creatinine level and urinary findings, a control is sufficient every few days.
Adequate fluid support should be provided in all patients (up to 2-3 liters per day). Patients with chronic liver disease should be especially observed. When applied in high volumes, it can change coagulation properties and prothrombin time (PZ), partial thromboplastin time (PTZ), bleeding and clotting times may be temporarily extended, dilution of plasma proteins and hematocrit reduction may occur.

A slight decrease in platelet and hemoglobin levels may be observed in patients undergoing repeated leukapheresis due to the plasma-expanding effect of HES. The hemoglobin level usually returns to normal within 24 hours. Hemodilution with HES solutions in isotonic sodium chloride may cause total protein, albumin, calcium and fibrinogen values to decrease for 24 hours.

In allergic patients, compensated heart failure, decreased kidney function, chronic liver disease, hypernatremia or hyperchloremia should be used with caution in cases of milder hemorrhagic diathesis.

Crystalloids should be preferred in cases of dehydration with extracellular space losses.

In cases of fibrinogen deficiency, HESAT 6%can only be given until blood is obtained in life- threatening emergencies.

During application, the patient's fluid and electrolyte balance should be checked.

Despite the possibility of possible incompatibility reactions, the first 10-20 mL of the solution should be administered slowly to the patient under close monitoring.

Rarely, anaphylactic or allergic reactions can occur. When hypersensitivity

reactions such as periorbital edema, urticaria and distressed breathing are seen, the infusion should be stopped and patients should be followed up intensively.

Precautions to take when adverse effects are seen
• Skin manifestations: Antihistamines
• Hypotension and tachycardia: Corticosteroid
• Syncope attacks, shock and bronchospasm: Adrenaline, high dose cortisone, oxygen and another volume-expanding intravenous solution
• Heart or respiratory arrest; reanimation attempts

In cases of such severe adverse effects, 24-hour follow-up or treatment in the intensive care unit is recommended.

In cases where circulating blood loss exceeds 20-25%, blood transfusion should be performed.

An increase in serum amylase levels may be seen after HESAT 6%application. This happens because it is related to the formation of a high molecular enzyme substrate complex, and because of its complex size it is slowly eliminated. Therefore, although this amylase height is not pathological, care must be taken during the diagnosis of pancreatitis.

Care should be taken to avoid contamination during the addition of other drugs to the solution.

This medicinal product contains 15.4 mmol sodium per 100 mL. This should be considered for patients on a controlled sodium diet.

Pediatric population:
Data in children are limited, so HES products are not recommended for use in this population.

4.5. Interaction with other medicinal products and other forms of interaction

It may prolong bleeding time when used with heparin or oral anticoagulants.

Patients receiving beta blocker and vasodilator therapy should be careful in terms of systemic blood pressure and heart rate.
Some clinical and biochemical measurements of HESAT 6%can be affected (eg glucose, protein, sedimentation rate, fatty acids, cholesterol, isosorbide-dehydrogenase, urine density).
Other infusion solutions, concentrated fluids used in the preparation of the infusion and when it is necessary to add injectable medicines in powder form, it should be checked with the naked eye if the possibilities are not possible with sensitive methods.(however, there may also be invisible chemical, hence therapeutic incompatibilities). There is no experience of its interaction with nutrients.

4.6. Pregnancy and lactation

General recommendation

Pregnancy category: C

Women with childbearing potential/Contraception
It has no known negative effects.

Pregnancy

Sufficient data are not available on the use of HESAT 6%in pregnant women.
Studies on animals are insufficient in terms of effects on pregnancy / and-or / embryonal / fetal development / and or / birth / and-or / postpartum development (see section 5.3). The potential risk for humans is unknown. No embryotoxic effects have been reported until now. Since there is no experience with its effect on pregnant women, it should be decided whether to use it or not, considering the benefits and possible drawbacks of HESAT 6%.

It can only be used in life-threatening indications during early pregnancy.

It should be taken into consideration that it may cause anaphylactic reactions and damage the fetus brain as a result of its use during pregnancy.

Lactation
It is not known whether hydroxyethyl starch passes into breast milk.

4.7. Effects on ability to drive and use machines

There is no known effect on driving and the use of machine.

4.8. Undesirable effects

The frequency classification of adverse drug reactions is 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); Not known (cannot be estimated from the available data)

Infections and infestations

Rare: Flu-like symptoms such as growth in the submaxillary and parotid salivary glands, headache, muscle pain and edema in the lower extremities (as a sign of hypersensitivity).
Immune system diseases

Rare: Pruritus, urticaria (as a sign of hypersensitivity)

Cardiac diseases

Very rare: Cardiac arrest (as a sign of hypersensitivity)

Vascular diseases

Very rare: Shock (as a sign of hypersensitivity)

Respiratory, thoracic and mediastinal diseases

Very rare: Respiratory arrest (as a sign of hypersensitivity)

Gastrointestinal diseases

Rare: Vomiting (as a sign of hypersensitivity)

Skin and subcutaneous tissue disorders

Not known: Itching (usually dose-dependent and resistant to treatment. Itching may continue after discontinuation of treatment).
Hepato-biliary diseases

Not known: hepatic damage.

Musculoskeletal, ligament and bone disorders

Rare: Pain in extremities, edema (as a sign of hypersensitivity)

Kidney and urinary diseases

Rare: Kidney pain (it is necessary to continue infusion with another fluid and look at serum creatinine levels).
Not known: renal damage.

General disorders and diseases related to the application site

Rare: fever, chills (as a sign of hypersensitivity)

Studies

Not known: Prothrombin time (PZ), partial thromboplastin time (PTZ), temporary elongation in bleeding and clotting times; dilution of plasma proteins, drop in hematocrit (when applied in high volumes); an increase in serum amylase levels.

When any signs of hypersensitivity are encountered, the infusion should be stopped immediately and necessary precautions taken (such as

antihistamines, adrenaline, corticosteroids, oxygen and airway keeping open).

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9. Overdose and therapy

Rapid infusion over treatment doses causes increased blood volume, resulting in pulmonary edema and decompensated heart. It also causes circulatory disturbance and prolonged circulation time.

Higher doses of HESAT 6%cause a decrease in hemoglobin, hematocrit and plasma protein concentration as a result of hemodilution. Values below 10 mg / dL for hemoglobin and below 27% for hematocrit are considered critical. In cases where the total protein level falls below 5 g / dL, it may be necessary to supplement albumin.
Excessive hemodilution can disrupt oxygen transport.
In case of overdose; the infusion should be stopped. The patient showing signs of cardiopulmonary decompensation should be followed closely and liver and kidney functions should be monitored.

Patients should be carefully monitored in terms of fluid electrolyte balance and hemorrhagic diathesis and appropriate treatment methods should be applied when necessary.

Hypervolemic patients can be treated with diuretics. After the general condition of the patients has improved, treatment with HESAT 6%can be continued again at low speeds under careful observation.

5. Pharmacological properties

5.1. Pharmacodynamic properties

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

Hydroxyethyl starch is produced by hydroxyethylation following partial hydrolysis of amylopectins. It is characterized by the degree of substitution by molecular weight. Its average molecular weight is up to 200,000 Daltons. A 0.5 degree of substitution indicates that five of the average 10 units of glucose in the amylopectin molecule are hydroxyethylated. Due to its structural similarity close to the glycogen molecule, it is compatible with the body and the risk of anaphylaxis is very low.

HESAT 6%is a solution with a slight hyperoncotic pressure effect with

isooncotic. It has an expansion effect that corresponds to more than 100% of the volume originally given. However, it does not cause volume changes in the following period and can be used in the clinic as an iso- osmotic intravenous solution.

The central venous pressure, which is low as a result of HESAT 6%application, increases in direct proportion to the volume given and reaches normal values. The average body retention time of a normal adult with a kidney function of 500 mL for 4 hours and 10% HES solution is 5-6 hours.

The colloidal properties of 6% HES are similar to the albumin in human blood. After intravenous infusion of HES solutions, it provides expansion in plasma volume slightly greater than the amount applied with colloidal osmotic effect. In hypovolemic patients, maximum plasma volume expansion is achieved within minutes of termination of the infusion. The duration of the volume- expanding effect depends on the distribution of the solution in the body, the plasma volume before administration, the renal clearance rate. In hypovolemic patients, there may be a temporary increase in arterial and venous pressure, cardiac index, workload index of the heart and pulmonary wedge pressure after HES application. HES increases erythrocyte sedimentation rate when mixed with whole blood.

HESAT 6%is suitable for short and medium-term volume replacement therapy and hemodilution, with both a controlled and short-term (about 3 hours) volume-expanding effect and preferred rheological effects (reduced blood viscosity, hematocrit and platelet aggregation).

5.2. Pharmacokinetic properties

Absorption:

After HESAT 6%infusion, the hydroxyethyl starch concentration in the body increases to 94% and decreases to 68%, 42%, 27% and 16%, respectively, after the 1st, 3rd, 6th and 12th hours.

Distribution:

HES molecules with a molecular size below 50,000 are quickly eliminated through the kidneys. Approximately 70% of it is released in the urine within 24 hours. Larger molecules break down; 90% of this dose is eliminated (the average half-life is 17 days; the remaining half of the 10% is 48 days). The hydroxyethyl group remains intact to be attached to the glucose units. Molecules partially out of the vein are stored in the RES (reticulo endothelial system).

Even months later, the presence of molecules in RES has been demonstrated, but there is little evidence of its effect on RES functions.

Biotransformation:

A small amount of non-hydroxyethylated starch molecules are slowly enzymatically broken down into glucose. Most of them are excreted by the renal route after enzymatic changes.

Elimination:

The molecular weight of the hydroxyethyl starch applied is less than 50,000 and is rapidly eliminated through the kidneys. Approximately 70% of the dose administered in this way is excreted in the urine within 24 hours. Larger molecules break down and 90% are excreted in the urine.

5.3. Preclinical safety data

In acute toxicity studies, intravenous doses of LD50 have been reported as 8,280 mg / kg in rats, 20,300 mg / kg in mice and 8,460 mg / kg in rabbits. In addition, changes in motor activity in mice have been reported.

In chronic toxicity studies, 675 mg / kg of intravenous administration in rats has been shown to cause specific developmental anomalies in the musculoskeletal system and developmental toxicity in the non-embryo structures of the embryo or fetus (eg placenta, cord). Intravenous administration at a dose of 200 mg / kg in rabbits leads to fetotoxicity (eg, contraction in the fetus) except death, while doses of 100 mg / kg led to specific developmental anomalies in the musculoskeletal system. Hydroxyethyl starch has also been shown to cause reproductive toxicity (decrease in weight gain in newborns) in chronic exposure with doses of 420 mg / kg administered intravenously in mice.

Teratogenic effect was not observed. No data were obtained in the mouse and rabbit experiments indicating that it harms the fetus. However, caution should be exercised during pregnancy and lactation periods.

Researches in rabbits, medical errors such as intravenous infusion and intravascular and intraarterial infusion do not cause damage to tissues.

6. Pharmaceutical particulars

6.1. List of Excipients

Sodium Chloride
Hydrochloric Acid
Sodium Hydroxide
Water for injection

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

Discard any unused solution immediately after first use.

6.4. Special precautions for storage

Do not store above 30°C. Do not freeze.

6.5. Nature and contents of container

The bags are composed of Polyolefin and contain Hydroxyethyl starch 6% solution. The bags are overwrapped with a protective over pouch which serves only to provide physical protection to the bag. Outer carton contents: 10 bags of 250ml (15g in 250ml) 10 bags of 500ml (30g in 500ml) Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

For single use only. To be used immediately after the bag is opened. Do not use Hesat 6% after expiry date. Any unused solution should be discarded. Use only clear, particle-free solutions and undamaged containers. Remove the overwrap from the Polyolefin bag prior to use. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Marketing authorisation holder

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Manufacturing site address

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8. Marketing authorisation number

CTD9936

9. DATE OF FIRST AUTHORISATION

03-Aug-2023

10. Date of revision of the text

14-Sep-2023

11. Dosimetry:

Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals

Not Applicable