534/NP53446/1018

Directions for Use

B. Braun Medical SA · 1023 Crissier, Switzerland

Hydroxyethyl Starch (130/0.4)

Tetraspan 6%

6% w/v solution for IV infusion (in ion adapted solution)
Plasma Expander/ Blood Substitute

Composition

1000 mL of solution contain:	
Hydroxyethyl starch (HES)	60.0 g
(Molar substitution: 0.42)	
(Average molecular weight: 130,000 Da)	
Sodium chloride	6.25 g
Potassium chloride	0.30 g
Calcium chloride dihydrate	0.37 g
Magnesium chloride hexahydrate	0.20 g
Sodium acetate trihydrate	3.27 g
L-Malic acid	0.67 g
Electrolyte concentrations:	
Sodium	140 mmol/L
Potassium	4.0 mmol/L
Calcium	2.5 mmol/L
Magnesium	1.0 mmol/L
Chloride	118 mmol/L
Acetate	24 mmol/L
L-Malate	5.0 mmol/L

Excipients:
Sodium hydroxide (for pH adjustment)
Water for injections

Pharmaceutical form
Solution for infusion.
Clear, colourless, aqueous solution.

pH:	5.6–6.4
Theoretical osmolarity:	296 mOsmol/L
Acidity (titration to pH 7.4):	<2.0 mmol/L

Indications
Treatment of hypovolaemia due to acute blood loss. (see sections "Dosage", "Contraindications" and "Special warnings and precautions for use")

Dosage
Use of Hydroxyethyl starch should be restricted to the initial phase of volume resuscitation with a maximum time interval of 24 h.

The daily volume and the infusion rate depend on the volume of blood loss and on how much fluid is required to restore haemodynamic parameters.
The first 10-20 mL should be infused slowly and under careful monitoring of the patient so that any anaphylactic/ anaphylactoid reaction can be detected as early as possible.
Prior to administration of HES, the indication of hypovolaemia should be confirmed, e.g. by assessing the positive fluid responsiveness of the patient.
The volume limitations given by the degree of haemodilution should be observed, see sections "Special warnings and precautions for use" and "Undesirable effects".

Adults
Maximum daily volume:
If the patient is hypovolaemic, e.g. fluid responsive, up to 50 mL/kg body weight (BW) (equivalent to 3.0 g hydroxyethyl starch per kg BW) can be administered. This is equivalent to 3500 mL Tetraspan 6% for a patient weighing 70 kg.
If it is not possible to monitor the haemodynamic status of the patient, the dose has to be limited to 30 mL per kg body weight.

Maximum infusion rate:
The maximum infusion rate depends on the clinical situation. Patients in acute shock can be given up to 20 mL per kg BW per hour (equivalent to 0.33 mL per kg BW per min or 1.2 g hydroxyethyl starch per kg BW per hour).
In life-threatening situations, 500 mL can be administered rapidly as a pressure infusion. See also section 'Method of administration'.
The lowest possible effective dose should be applied. Treatment should be guided by continuous haemodynamic monitoring so that the infusion is stopped as soon as appropriate haemodynamic goals have been achieved.
The maximum recommended daily dose must not be exceeded.

Elderly patients
See section "Special warnings and precautions for use".

Paediatric population:
Data are limited in children therefore it is recommended not to use Hydroxyethyl starch products in this population.
The safety and efficacy of Tetraspan 6% in the paediatric population have not yet been fully established.
Currently available data are described in section "Undesirable effects" and "Pharmacodynamic properties" but no recommendation on a posology can be made.

Method of administration
Intravenous use.
In the case of a rapid infusion under pressure, using plastic container with air space inside, the container and infusion set should be emptied of air before the infusion is started. This is to avoid the risk of air embolism that might otherwise be associated with the infusion.

Contraindications
- hypersensitivity to the active substances or to any of the other excipients listed.
- sepsis
- burns
- renal impairment or renal replacement therapy
- intracranial or cerebral haemorrhage
- critically ill patients (typically admitted to the intensive care unit)
- hyperhydration
- pulmonary oedema
- dehydration
- hyperkalaemia
- severe hypernatraemia or severe hyperchloraemia
- severely impaired hepatic function
- congestive heart failure
- severe coagulopathy
- organ transplant patients

Special warnings and precautions for use
Because of the risk of allergic (anaphylactic/ anaphylactoid) reactions, the patient should be monitored closely and the infusion instituted at a low rate. (See section "Undesirable effects").
The indication for volume replacement with Hydroxyethyl starch has to be considered carefully, and haemodynamic monitoring is required for volume and dose control. (See also section "Dosage".)
Hydroxyethyl starch solutions should only be used when crystalloids alone are not considered sufficient.
Volume overload due to overdose or too rapid infusion must always be avoided. The dosage must be adjusted carefully, particularly in patients with pulmonary and cardiocirculatory problems.
Serum electrolytes, fluid balance and renal function should be monitored closely. Electrolytes and fluids should be substituted according to individual requirements.
Hydroxyethyl starch products are contraindicated in patients with renal impairment or renal replacement therapy (see section "Contraindications"). The use of Hydroxyethyl starch must be discontinued at the first sign of renal injury. Monitoring of renal function is recommended.
Particular caution should be exercised when treating patients with impaired hepatic function or in patients with blood coagulation disorders.
Severe haemodilution resulting from high doses of Hydroxyethyl starch solutions must also be avoided in the treatment of hypovolaemic patients.
In the case of repeated administration, blood coagulation parameters should be monitored carefully. Discontinue the use of Hydroxyethyl starch at the first sign of coagulopathy.
In patients undergoing open heart surgery in association with cardiopulmonary bypass the use of Hydroxyethyl starch products is not recommended due to the risk of excess bleeding.
Sufficient fluid intake must be ensured.

Elderly patients
Elderly patients, who are more likely to suffer from cardiac insufficiency and renal impairment, should be closely monitored during treatment, and the dosage should be carefully adjusted, in order to avoid cardiocirculatory and renal complications resulting from hypervolaemia.

Paediatric population:
Data are limited in children therefore it is recommended not to use Hydroxyethyl starch products in this population. (see section "Dosage", "Undesirable effects" and "Pharmacodynamic properties")

Influence on laboratory tests
Transiently raised alpha-amylase levels can occur after administration of solutions with hydroxyethyl starch. This should not be interpreted as a sign of pancreatic injury (see section "Undesirable effects").

Interaction with other medicinal products and other forms of interaction

Medicinal products reducing renal function
The concomitant use of Hydroxyethyl starch solutions with potential nephrotoxic medicinal products e.g. aminoglycoside antibiotics may potentiate their adverse effect on the kidneys.

Medicinal products causing potassium or sodium retention
As the product contains electrolytes itself consideration should be given to the concomitant administration of medicinal products that can cause potassium or sodium retention.

Digitalis glycosides
Raised calcium levels can increase the risk of toxic effects of digitalis glycosides.

Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of Hydroxyethyl starch in pregnant women. Animal reproduction toxicity studies with similar products have revealed vaginal bleeding, embryotoxicity and teratogenicity after repeated treatment in test animals (see section "Preclinical safety data").
Harmful effects on the foetus can occur with Hydroxyethyl starch-related anaphylactic/anaphylactoid reactions in treated pregnant women.
Tetraspan 6% should only be used during pregnancy if the potential benefits outweigh the possible risks to the foetus. This should be borne in mind in particular if treatment with Tetraspan 6% is being considered during the first trimester.
Special care must be taken to avoid overdose resulting in hypervolaemia with consecutive pathological haemodilution and foetal hypoxia (see section "Preclinical safety data").

Breast-feeding
It is unknown whether Hydroxyethyl starch passes into breast milk. Caution should be exercised on administration to breast-feeding women. The temporary cessation of breast-feeding may be considered.

Fertility
No data available.

Effects on ability to drive and use machines
This medicinal product has no influence on the ability to drive and use machines.

Undesirable effects

General
The most common side effects observed are directly related to the therapeutic effect of starch solutions and the volume given, i.e. dilution of the blood as a result of the filling of the intravascular space without administering blood components at the same time. Coagulation factor dilution can also occur. Serious anaphylactic/anaphylactoid reactions have been reported and may require immediate action (please refer also to the section 'Anaphylactic/Anaphylactoid reactions' below).
Hypersensitivity reactions are not dose-dependent.

	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)	Frequency not know (cannot be estimated from the available data)
Blood and lymphatic system disorders	Decreased haematocrit, reduced concentration of plasma proteins	Dilution of coagulation factors, prolongation of bleeding time and aPTT, reduced level of FVIII/vWF complex (1) (see section "Special warnings and precautions for use")			
Hepatobiliary disorders					Hepatic injury
Immune system disorders				Anaphylactic/ anaphylactoid reactions of various degrees (see "Anaphylactic/ anaphylactoid reactions" below)	
Renal and urinary disorders					Renal injury
General disorders and administration site conditions			Itching which responds poorly to any therapy (2)		
Investigations	Increased serum α-amylase levels (3)				

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(1) Effects occur after administration of relatively large volumes of hydroxyethyl starch and can affect blood coagulation. See section "Special warnings and precautions for use".
(2) This itching can occur several weeks after the end of the starch infusions and can persist for months. The probability of this undesirable effect has not been sufficiently studied for Tetraspan 6%.
(3) This effect is a result of the formation of an amylase complex of Hydroxyethyl starch with delayed renal and extrarenal elimination. This should not be misinterpreted as evidence of a pancreatic disorder.

Paediatric population
In clinical studies it was shown that frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Information on particular undesirable effects

Anaphylactic/ anaphylactoid reactions
After administration of Hydroxyethyl starch, anaphylactic/anaphylactoid reactions of various degrees can occur which are not dose-dependent. Therefore, all patients receiving starch infusion should be monitored closely for anaphylactic/anaphylactoid reactions. In the event of an anaphylactic/anaphylactoid reaction, the infusion should be discontinued immediately and the usual acute treatment initiated.
It is not possible to predict by tests which patients may be expected to suffer an anaphylactic/anaphylactoid reaction nor is it possible to predict the course and severity of such a reaction. Prophylaxis with corticosteroids has not been shown to have a preventive effect.

Overdose

Symptoms
Overdose with Tetraspan would lead to unintended hypervolaemia and circulatory overload with a significant fall in haematocrit and plasma proteins. This may be associated with consecutive impairment of heart and lung function (pulmonary oedema).

Treatment
In the case of an overdose, the infusion must be discontinued immediately and administration of diuretics considered. The patient should be treated symptomatically and electrolytes should be monitored.

Pharmacodynamic properties
Pharmacotherapeutic group: Blood substitute and plasma proteins,
ATC code: B05A-A07

Mechanism of action
Tetraspan is a colloidal plasma volume substitute containing Hydroxyethyl starch (HES) in a balanced electrolyte solution. The average molecular weight is 130,000 Daltons and its molar substitution is 0.42.
Tetraspan 6% is iso-oncotic, i.e. the increase in the intravascular plasma volume is equivalent to the infused volume.
With isovolaemic administration, the volume expanding effect persists for at least 4-9 hours. The duration of the volume effect is primarily based on molar substitution and to a lesser extent on the average molecular weight. Intravascular hydrolysis of Hydroxyethyl starch polymers results in a continuous release of smaller molecules which also are oncotically active before they are excreted via the kidneys.
Tetraspan 6% may lower the haematocrit and the plasma viscosity.
Tetraspan also has a favourable effect on the microcirculation by altering the flow characteristics of the blood.
The cation pattern in the crystalloid component of Tetraspan 6% is adapted to physiological plasma electrolyte concentrations. The anion pattern is a combination of chloride, acetate and L-malate, the purpose of which is to minimise the risk of hyperchloraemia and acidosis. Additions of acetate and L-malate instead of lactate anions are intended to reduce the risk of lactic acidosis.

Paediatric population
An European multicentric prospective observational postauthorization safety study (PASS) has been conducted to evaluate the use of Hydroxyethyl starch in Venofundin 6% and Tetraspan 6% in children (n= 1130) up to 12 years undergoing surgery.
The safety of Hydroxyethyl-starch in the perioperative phase in children was evaluated based on possible adverse drug reactions and acid-base, electrolyte, and haemoglobin changes. No serious and no severe adverse drug reactions directly related to Hydroxyethyl starch were observed. The rate of adverse reactions was dose dependent but no age relationship could be demonstrated (see section "Undesirable effects").
It was concluded that for perioperative use a dose of up to 20 mL/ kg body weight seems to be safe in children.

Pharmacokinetic properties

General
The characteristics of the electrolytes contained in Tetraspan are the same as in normal physiology.

Absorption
As Tetraspan is administered intravenously, the bioavailability is 100%.

Distribution
Hydroxyethyl starch is a mixture of several different molecules with a different molecular weight and degree of substitution. Like all colloids, hydroxyethyl starch, too, is temporarily stored particularly in the cells of the mononuclear phagocyte system (MPS), however, without producing any irreversible toxic effects on liver, lungs, spleen and lymph nodes. Minor quantities of the stored active substance in the skin are still histologically detectable several months after administration. Such storage phenomena are assumed to be the cause for the itching.
Hydroxyethyl starch does not pass the blood-brain barrier. No relevant Hydroxyethyl starch concentrations were detected in the umbilical cord excluding the possibility of a maternal-foetal transfer of Hydroxyethyl starch.

Biotransformation/Elimination
Elimination is dependent on the degree of substitution and to a lesser extent on molecular weight. Molecules which in terms of size are below the so-called renal threshold are excreted by glomerular filtration. Larger molecules are first degraded by alpha-amylase before they are excreted renally. The rate at which the molecules are degraded decreases with increasing degree of substitution of the molecules.
After a single infusion of 1000 mL Tetraspan 6%, plasma clearance is 19 mL/min and AUC 58 mg×h ×mL^{-1}. The terminal serum half-life is about 4-5 hours.

Pharmacokinetics in paediatric patients
No pharmacokinetic data from treatment of children are available.

Preclinical safety data
No toxicological animal studies have been conducted with Tetraspan 6%. Published animal toxicological studies with repeated hypervolaemic treatment with similar Hydroxyethyl starch products have revealed bleeding and extensive histiocytosis (accumulation of foam-like histiocytes/macrophages) in several organs with an increase in weight of the liver, kidneys and spleen. Infiltration of fat and vacuolation of organs as well as elevations of plasma AST and ALT have been reported. It has been suggested that some of the effects described were caused by haemodilution, increased circulatory load and uptake and accumulation of starch in phagocytic cells.
Similar Hydroxyethyl starch products have been reported to be non-genotoxic in standard tests.
Reproductive toxicity studies of Hydroxyethyl starch products showed vaginal bleeding and signs of embryo-/foetotoxicity and teratogenicity associated with repeated administration to test animals. These effects may be due to haemodilution and result in foetal hypoxia and hypervolaemia. Bleeding can also be in part a direct consequence of the effects that Hydroxyethyl starch has on the blood coagulation.

Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life
The product must not be used beyond the expiry date stated on the labelling.

After first opening
The product should be administered immediately after connecting the container to the administration set.

Special precautions for storage
Do not freeze.
Do not store above 30° C.

Presentation
DR-XY35391: 500 mL Ecobag

Special precautions for disposal and other handling
No special requirements for disposal.
Administration should commence immediately after connecting the container to the administration set.
For single use only.
Use as soon as the primary packaging is opened. Any unused contents should be discarded.
Use only if the solution is clear, colourless and the packaging is undamaged.
Do not re-connect partially used containers.

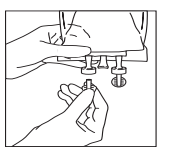
Caution:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
Seek medical attention immediately at the first sign of any adverse drug reaction

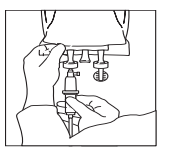
Date of revision:
10.2018

Instructions for Handling the Ecobag Container

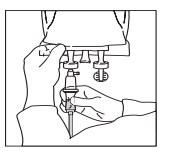
1. Preparation of the container
- Check container and closure are intact.
- Check contents for clarity and discoloration
- Open container by twisting off the corresponding toggle. The opened infusion port site is sterile.
  (⇩ ⇨ Infusion port)
  (⇩ ⇨ Additive port)



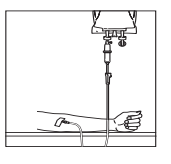
2. Gravity infusion
- Close air vent and roller clamp of infusion set.
- Insert infusion set.



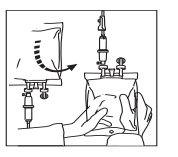
- Fill half of drip chamber.
- Fill infusion tube avoiding bubbles.



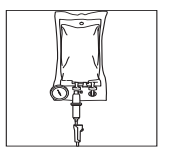
- Connect infusion tube to cannula/catheter.
- Start infusion, leaving air vent closed.



or 2. Pressure infusion
- Insert infusion set.
- Hold container upright.
- Leave roller clamp open, expel air from container and fill half of drip chamber.
- Turn container and expel air from infusion set.
- Close roller clamp.



- Place container in pressure cuff.
- Build up pressure.
- Open roller clamp and start infusion.



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Lätus: 1245
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