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Directions for Use

B. Braun Melsungen AG · 34209 Melsungen, Germany

Tetraspan 6%

solution for infusion

Composition
1000 ml contains

Active substances:		
Poly(O-2-hydroxyethyl) starch (HES) (Molar substitution: 0.42) (Average molecular weight: 130,000 dalton)	60.0 g	
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	
Malic acid	0.67 g	
Electrolyte concentration:		
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
Malate	5.0	mmol/l
pH:	5.6 - 6.4	
Theoretical osmolarity:	296 mOsmol/l	
Acid titre:	< 2.0 mmol/l	

Excipients:
Sodium hydroxide (for pH adjustment), Water for Injections

Pharmaceutical form
Solution for infusion.

Pharmaco-therapeutic group
Blood substitutes and plasma protein fractions, ATC code B05A A07

Pharmacological Properties

Pharmacodynamic Properties
Tetraspan 60 mg/ml is a colloidal plasma volume substitute containing 6% Hydroxyethyl starch (HES) in a balnced electrolyte solution. The mean molecular weight is 130,000 Daltons and its molar substitution is 0.42.
Tetraspan 60 mg/ml is iso-oncotic, i.e. the increase in the intravascular plasma volume is equivalent to the infused volume.
The duration of the volume effect is primarily based on molar substitution and to a lesser extent on the mean molecular weight. Intravascular hydrolysis of HES polymers results in a continuous release of smaller molecules which in turn are oncotically active before they are excreted via the kidneys.
Tetraspan 60 mg/ml may lower haematocrit and plasma viscosity.
With isovolaemic administration, the volume expanding effect is maintained for at least 6 hours.
The cation pattern in the crystalloid component Tetraspan 60 mg/ml is adapted to physiological plasma electrolyte concentrations. The anion pattern is a combination of chloride, acetate and malate, the purpose of which is to minimise the risk of hyperchloraemia and acidosis. Addition of acetate and malate instead of lactate anions are intended to reduce the risks of lactic acidosis.

Experience from treatment of children
The experience from treatment of children is limited. If Tetraspan 6% is used in children the dose should be individualised, taking the haemodynamic status and the underlying disease into account. No pharmacokinetic data from treatment of children are available.

Pharmacokinetic Properties
Hydroxyethyl starch is a mixture of several various molecules with a different molecular weight and degree of substitution. Elimination is dependent on molecular weight and degree of substitution. Molecules smaller than the so-called renal threshold are eliminated by glomerular filtration. Larger molecules are degraded by alpha-amylase and are thereafter eliminated renally. The rate of degradation decreases with increased degree of substitution.
Approximately 50% of the administered dose is excreted into urine within 24 hours. After a single infusion of 1000 ml Tetraspan 60 mg/ml, plasma clearance is 19 ml/min and AUC 58 mg x h/ml. The terminal serum half-life is about 12 hours.

Preclinical safety data
No toxicological animal studies have been conducted with Tetraspan 60 mg/ml. Published toxicological studies with low molecular weight and low substituted HES in general reveal no special hazardous for humans.
Similar HES products have been reported to be non-genotoxic in standard tests.
Reproductive toxicity studies of HES products showed vaginal bleeding and signs of embryo-/foetotoxicity and teratogenicity associated with repeated administration of laboratory animals. These effects may be related to haemodilution and result in foetal hypoxia and hypervolaemia. Bleeding may partly also be related to direct effects of HES on the blood coagulation. Haemodilution due to circula-tory overload should always be avoided when treating hypovolaemic patients.

Indications
In case of hypovolaemia a crystalloid solution should first be given. Hydroxyethyl starch (HES) is indicated for the treatment of hypovolaemia if patient does not respond to crystalloid solution.

Contraindications
- Do not use Hydroxyethyl starch (HES) products, in critically ill adult patients including patients with sepsis due to increased risk of mortality and renal replacement therapy
- Do not use HES products in patients with severe liver disease
- Do not use HES products in patients with renal failure with oliguria or anuria not related to hypovolaemia
- Do not use HES products in patients receiving dialysis treatment
- Hyperhydration states including pulmonary edema
- Intracranial bleeding
- Hyperkalaemia
- Severe hypernatremia or severe hyperchloremia
- Hypersensitivity to hydroxyethyl starch or to any of the excipients
- Congestive cardiac failure

Special warnings and precautions for use
Avoid use in patients with pre-existing renal dysfunction.
Discontinue use of HES products 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 administrations of HES products.
In severe dehydration a crystalloid solution should be given first.
Monitor liver function in patients receiving HES products.
Monitor kidney function, fluid balance and serum electrolytes.
Adequate fluid intake must be ensured.
Volume overload from overdosage should always be avoided. Dosage should be carefully adjusted, especially in patients with cardiac insufficiency.
Elderly patients with hypovolaemia should be throughly monitored, and the dosage should be adapted, in order to avoid impairment of renal function.
Particular caution should be exercised in patients with hepatic insufficiency.
Because of the possibility of allergic (anaphylactic/anaphylactoïd) reactions, appropriate monitoring of patients is necessary, and a slow infusion rate should be initiated (See section **Undesirable effects**).
Elevated serum alpha-amylase concentrations may be observed temporarily following administration of HES solutions and must not be considered diagnostic of impaired pancreatic function (See section **Undesirable effects**).

Pregnancy and lactation
No adequate data are available for Tetraspan from the treatment of pregnant women. Tetraspan has not been tested in reproductive toxicology studies in animals, but studies of similar products have revealed vaginal bleeding, embryotoxic and teratogenic effects after repeated treatment of laboratory animals.
HES-related anaphylactic reactions in treated pregnant women may have harmful effects on the fetus.
Tetraspan should be used in pregnant women only if the anticipated benefits outweigh the potential risk to the fetus; this is especially to be considered when administration of Tetraspan in the first three months of pregnancy is planned.
As it is not known whether the modified starch in Tetraspan is excreted in breast milk, caution should be exercised when administering this product to breastfeeding mothers. Temporary interruption of breastfeeding may be considered.

Interactions
No interactions with other drugs or nutritional products are known to date.
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Dosage
The daily dose and infusion rate depend on the extent of blood loss, maintenance or restoration of hemodynamic parameters.
The first 10 – 20 ml should be infused slowly and with careful patient monitoring so that a possible anaphylactoid reaction can be detected as early as possible.

Maximum infusion rate:
The maximum infusion rate depends on the clinical situation. Patients in acute shock may be administered up to 20 ml per kg of body weight per hour (equivalent to 0.33 ml/kg/min or 1.2 g of hydroxyethyl starch per kg of body weight per hour). In life-threatening situations, 500 ml may be administered by manual pressure infusion. Also see "*Method of administration and duration of therapy*" below.

Maximum daily dose:
Up to 50 ml of Tetraspan per kg of body weight (equivalent to 3.0 g of hydroxyethyl starch per kg of body weight). This is equivalent to 3,500 ml of Tetraspan for a 70-kg patient.
The safety and efficacy of Tetraspan in children have not been studied. Therefore, Tetraspan should be used in children only after careful benefit/risk assessment, and with caution.

Treatment of children:
Limited clinical data on the use of low molecular and low substituted HES (HES 130/0.4) in children is available. If Tetraspan is used in children the dose should be individualised, taking the haemodynamic status and the underlying disease into account.

Method of administration and duration of therapy:
For intravenous use.
If administration is by rapid infusion under pressure, all air must be withdrawn from the plastic container and infusion set prior to infusion, as otherwise there is a risk of producing air embolism during infusion.
The duration of therapy depends on the duration and extent of hypovolemia, the hemodynamic effects of the administered treatment, and the level of hemodilution.

Overdose
The greatest risk associated with an acute overdose is hypervolemia. In this case, the infusion must be stopped immediately, and administration of diuretics be considered.

Undesirable effects
Adverse reactions have been ranked under headings of frequency using the following convention:
Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000)
The most commonly reported adverse reactions are directly related to the therapeutic effects of starch solutions and the doses administered, *i.e.,* hemodilution resulting from expansion of the intravascular space without concurrent administration of blood components. Dilution of coagulation factors may also occur.
Hypersensitivity reactions, which are very rare, are not dose-dependent.

Blood and lymphatic system disorders
Very common:
Reduced hematocrit and decreased plasma protein concentrations as a result of hemodilution.
Common (dose-dependent):
Higher doses of hydroxyethyl starch cause dilution of coagulation factors and may thus affect blood clotting. Bleeding time and aPTT may be increased and FVIII/vWF complex levels may be reduced after administration of high doses. See 4.4 "Special warnings and special precautions for use".

Immune system disorders
Rare:
Anaphylactic reactions of various intensities. For details see "*Anaphylactic reactions*" below.

General disorders and administration site conditions
Uncommon:
Repeated infusions of HES for many days, especially when high cumulative doses are reached, usually lead to pruritus (itching) which responds very poorly to therapy. This pruritus may occur many weeks after discontinuing the starch infusions and may persist for months. The likelihood of this adverse effect has not been adequately studied for Tetraspan.

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Investigations
Very common:
The infusion of hydroxyethyl starch produces elevated serum α-amylase concentrations. This effect is the result of the formation of an amylase complex of hydroxyethyl starch with delayed renal and extrarenal elimination. It should not be misinterpreted as evidence of a pancreatic disorder.

Anaphylactic reactions
Anaphylactic reactions of various intensities may occur after administration of hydroxyethyl starch. All patients receiving starch infusions should therefore be closely monitored for anaphylactic reactions. In case of an anaphylactic reaction, the infusion must be stopped immediately and the usual emergency treatment instituted.
There are no tests to identify patients in whom an anaphylactic reaction is likely, nor can the outcome and severity of such a reaction in a given patient be predicted.
The prophylactic use of corticosteroids has not proved effective.

Note:
Patients should inform their doctor or pharmacist if they notice any side effect not mentioned in this leaflet.

Expiry date / Shelf life
The product must not be used beyond the expiry date stated on the labelling.
The product expected shelf life is 3 years.

Instructions for storage / use / handling
Do not freeze. Do not store above 30 °C.
For single use only. Use immediately after first opening and discard any unused product.
Use only clear solution, practically free from particles, from intact containers.

Date of last revision: 10.2014

Presentation:
Tetraspan 6%, 500 ml, Polyethylene Container

Reg No: DKI1396901149A1

Harus dengan resep dokter

Manufactured by:
B. Braun Medical SA
Route de sorge 9
1023 Crissier, Switzerland

Imported by:
PT. B. Braun Medical Indonesia
Jakarta, Indonesia

License Holder:
PT. Phapros Tbk., Indonesia

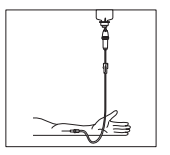
Further information

Pressure infusion from Ecoflac plus plastic containers:
If wished to administer by rapid infusion under pressure, all air must be withdrawn from the plastic container and infusion set prior to infusion.

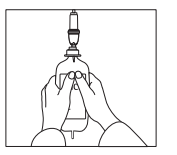
To expel air from the polyethlene container Ecoflac plus a vented giving set or a filtered venting needle should be used.

Instructions for Handling the Ecoflac plus Container

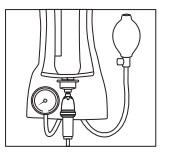
1. Gravity infusion
- Insert infusion set, fill half of drip chamber, fill infusion tube avoiding bubbles.
- Close air vent of infusion set.
- Connect infusion tube to cannula/catheter.
- Open clamp and start infusion with air vent closed



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

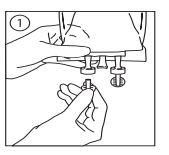


- Place container in pressure cuff.
- Build up pressure.
- Open clamp and start infusion.

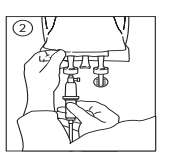


Instructions for Handling the Ecobag Container

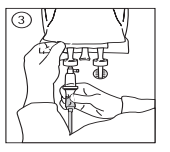
1. Preparation of the container
- Check container and closure are intact.
- Check contents for clarity and discoloration
- Open container by twisting off the corresponding toggle. The opened infusion port site is sterile.
  (⇨ Infusion port)
  (⇨ Additive port)



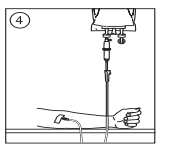
2. Gravity infusion
- Close air vent and roller clamp of infusion set.
- Insert infusion set.



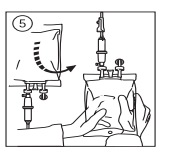
- Fill half of drip chamber.
- Fill infusion tube avoiding bubbles.



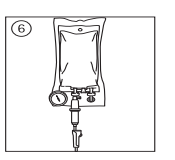
- Connect infusion tube to cannula/catheter.
- Start infusion, leaving air vent closed.



5. 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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