APPROVED PACKAGE INSERT

VOLULYTE®

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

VOLULYTE solution for infusion

COMPOSITION

Each 1 000 ml solution for infusion contains:

Poly (O-2-hydroxyethyl) starch	60,00 g
- Molar substitution 0,38 – 0,45	
- Mean molecular weight 130 000 Da	
Sodium acetate trihydrate	4,63 g
Sodium chloride	6,02 g
Potassium chloride	0,30 g
Magnesium chloride hexahydrate	0,30 g

Electrolytes:

Na^+	137,0 mmol/l
K^+	4,0 mmol/l
Mg^{++}	1,5 mmol/l
Cl^-	110,0 mmol/l
CH_3COO^-	34,0 mmol/l

Theoretical osmolarity: 286,5 mOsm/l

Titratable acidity: < 2,5 mmol NaOH/l

pH value 5,7 - 6,5

Inactive ingredients: Sodium hydroxide (for pH adjustment), hydrochloric acid (25 %) (for pH adjustment) and water for injections.

PHARMACOLOGICAL CLASSIFICATION

A 8.4 Plasma expanders

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

The active ingredient hydroxyethyl starch (HES 130/0,4) is a derivative of waxy maize starch mainly consisting of a glucose polymer (amylopectin) predominantly composed of α-1,4-connected glucose units with several α-1,6-branches.

Poly (O-2-hydroxyethyl) starch is an artificial colloid for volume replacement. Its pharmacological properties depend on the molar substitution by hydroxyethyl groups (0,4), the mean molecular weight (130 000 Da), the concentration (6 %), the substitution ratio (C_2/C_6 ratio) of approximately 9:1 as well as the dosage and infusion rate.

Infusion of 500 ml of a similar product containing HES 130/0,4 (6 %) in 0,9 % sodium chloride solution 30 minutes in volunteers results in a plateau-like non-expansive volume increase of approximately 100 % of the infused volume, which lasts for approximately 4 to 6 hours.

Isovolaemic exchange of blood with HES 130/0,4 (6 %) in 0,9 % sodium chloride solution maintains blood volume for at least 6 hours.

Pharmacokinetic properties

The mean *in vivo* molecular weight of HES 130/0,4 in the plasma is 70 000 – 80 000 Da immediately after infusion and remains above the renal threshold of 60 000 – 70 000 Da throughout the therapeutic period.

The volume of distribution is about 5,9 litres.

The HES 130/0,4 molecules are metabolised by plasma α-amylase before the degradation products smaller than the renal threshold are renally excreted.

Within 30 minutes of infusion the plasma level of poly (O-2-hydroxyethyl) starch is still 75 % of the maximum concentration.

After 6 hours the plasma level has decreased to 14 %. Following a single dose of 500 ml 6 **%** HES 130/0,4 the plasma levels almost return to baseline after 24 hours.

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 x h, which shows a non-linear pharmacokinetics. Plasma half-lives were $t_{1/2\alpha}$ = 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 increased by a factor of 1,7 (95 % confidence limits 1,44 and 2,07) in subjects with Cl_{Cr} < 50 ml/min compared to >50 ml/min. Terminal half-life and peak poly (O-2-hydroxyethyl) starch concentrations are not affected by renal impairment.

At Cl_{Cr} ≥ 30 ml/min, 59 % of the active ingredient could be retrieved in the urine, vs. 51 % at Cl_{Cr} 15 to 30 ml/min. Plasma levels of HES 130/0,4 almost returned to baseline levels 24 hours following infusion.

In a pharmacokinetic study, eight stable patients with end stage renal disease (ESRD) received a single dose of 250 ml (15 g) of HES 130/0,4 (6 %). 3,6 g (24 %) of the HES dose was eliminated during a 2-hour haemodialysis session (500 ml dialysate per minute, Filter HD Highflux FX 50, Fresenius Medical Care, Germany).

After 24 hours the mean HES plasma concentration was 0,7 mg/ml. After 96 hours the mean plasma concentration of HES was 0,25 mg/ml.

HES 130/0,4 (6 %) is contra-indicated in patients receiving dialysis treatment (see **CONTRA-INDICATIONS**). There is no data available for the use of VOLULYTE in dialysis.

Pharmacokinetic data in patients with hepatic insufficiency or in paediatric or geriatric patients are not available.

Effects of gender on the pharmacokinetics of HES 130/0,4 have not been studied.

INDICATIONS

VOLULYTE, in conjunction with crystalloids, is indicated for the treatment of adult and paediatric patients, excluding neonates, with acute hypovolaemia associated with trauma and/or surgery, to restore haemodynamic stability.

The underlying cause of the hypovolaemia should be corrected and the patient should be continuously monitored.

CONTRA-INDICATIONS

Do not use VOLULYTE in:

- Patients with known hypersensitivity to hydroxyethyl starches

- Critically ill patients with or without sepsis/septicaemia
- Severe burns
- Patients with moderate to severe renal impairment (CrCl < 50 mℓ/kg/min)
- Renal failure with oliguria or anuria not due to hypovolaemia
- Patients receiving dialysis treatment
- Patients with severe hepatic impairment (Child-Pugh class C)
- Patients with moderate to severe dehydration
- Over-hydration with or without pulmonary oedema
- Patients with congestive cardiac failure
- Patients with pre-existing coagulation or bleeding disorders
- Patients with intracranial bleeding
- Patients with severe hypernatraemia, severe hyperkalaemia or severe hyperchloraemia.

WARNINGS AND SPECIAL PRECAUTIONS

- Caution is advised with the use of VOLULYTE in organ transplant patients.
- VOLULYTE is not recommended for use in patients more than 65 years of age, due to insufficient data on safety and efficacy of HES solutions in this age group.
- Avoid fluid overload; adjust dosage in patients with cardiac or renal dysfunction.
- The duration of treatment with VOLULYTE should not exceed 24 hours.
- Generally, sufficient fluid should be administered in order to avoid dehydration.

- Particular care must be taken in patients with severe electrolyte imbalances, such as hyperkalaemia, hypernatraemia, hypermagnesaemia and hyperchloraemia.
- In metabolic alkalosis and in clinical situations in which alkalisation should be avoided, saline-based hydroxyethyl starch solutions, e.g. a similar product containing hydroxyethyl starch 130/0,4 in isotonic sodium chloride solution should be preferred to alkalising solutions such as VOLULYTE.

Anaphylactic/anaphylactoid reactions:

- Anaphylactoid reactions (hypersensitivity, influenza-like symptoms, bradycardia, tachycardia, bronchospasm, non-cardiac pulmonary oedema) have been reported with solutions containing hydroxyethyl starch such as VOLULYTE. If a hypersensitivity reaction occurs, administration of VOLULYTE should be discontinued immediately and the appropriate treatment and supportive measures should be undertaken until symptoms have resolved (see **SIDE EFFECTS**).

Renal dysfunction

- Discontinue use of VOLULYTE at the first sign of clinically relevant renal injury.
- Continue to monitor renal function for at least 90 days in those patients who are still hospitalised when conducting the monitoring as use of renal replacement therapy has been recorded up to 90 days after administration of VOLULYTE.

Coagulopathy

- Monitor the coagulation status in patients undergoing open-heart surgery in association with cardiopulmonary bypass as excess bleeding has been reported with HES solutions in this population. Discontinue the use of VOLULYTE at the first sign of clinically relevant coagulopathy.

Fluid equilibrium

- Fluid status and rate of infusion should be assessed regularly during treatment, especially in patients with cardiac insufficiency.

General

Clinical evaluation and periodic laboratory determinations are necessary to monitor fluid balance, serum electrolyte concentrations, kidney function, acid-base balance, haemoglobin**,** haematocrit, plasma proteins and coagulation parameters during prolonged parenteral therapy or whenever the patient's condition warrants such evaluation.

Particular care must be taken in patients with electrolyte abnormalities.

Monitor liver function in patients receiving VOLULYTE.

Effects on ability to drive and use machines

VOLULYTE has no influence on the ability to drive and use machines.

INTERACTIONS

None observed.

Caution is required during concomitant administration of medicines that can cause potassium or sodium retention.

Interference with laboratory tests:

As the concentration of serum amylase is increased as a result of administration of hydroxyethyl starch, this can interfere with the diagnosis of pancreatitis (see **SIDE EFFECTS)**.

At high dosages the dilutional effects may result in decreased levels of coagulation factors and other plasma proteins and a decrease in haematocrit (see **SIDE EFFECTS**).

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established.

Information on the use of VOLULYTE during labour or delivery is unknown with the exception of caesarean section.

It is not known whether VOLULYTE is excreted in human breastmilk.

Caution should be exercised when VOLULYTE is administered to a woman who is breastfeeding her baby.

DOSAGE AND DIRECTIONS FOR USE

VOLULYTE is not recommended for use in patients more than 65 years of age due to insufficient data on safety and efficacy of HES solutions in this age group.

For use as an intravenous infusion.

- The dose and rate of infusion depend on the patient's blood loss, on the maintenance or restoration of haemodynamics and on the haemodilution (dilution effect).
- The duration of treatment with VOLULYTE should not exceed 24 hours.

- The initial 10 - 20 ml should be infused slowly. Keep the patient under close observation for the possibility of anaphylactic/anaphylactoid reactions).

Adult dose:

- The maximum dose of 30 ml/kg in 24 hours should not be exceeded.

The dose in adolescents >12 years of age is the same as the adult dose.

Paediatric dose:

VOLULYTE should not be used in neonates (babies less than 1 month old).

The dosage in children < 12 years of age should not exceed 15 mℓ/kg in 24 hours (see **PHARMACOLOGICAL ACTION – Pharmacodynamic properties**).

Instructions for handling:

For single use only.

To be used immediately after the bag is opened.

Do not use VOLULYTE after the expiry date. Any unused solution should be discarded.

Any unused solution should be disposed of in accordance with local requirements.

Use only clear, particle-free solutions and undamaged containers.

Remove the overwrap from the polyolefin (Freeflex) bag prior to use.

Incompatibilities:

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

SIDE EFFECTS

The side 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).

Blood and lymphatic system disorders:

Rare: Disturbances of blood coagulation, such as increased haemorrhage can occur (see WARNINGS AND SPECIAL PRECAUTIONS).

Immune system disorders:

Rare: Anaphylactic/anaphylactoid reactions (hypersensitivity, influenza-like symptoms, bradycardia, tachycardia, bronchospasm, non-cardiac pulmonary oedema).

If a hypersensitivity reaction occurs, administration of VOLULYTE should be discontinued immediately and the appropriate treatment and supportive measures should be undertaken until symptoms have resolved (see WARNINGS AND SPECIAL PRECAUTIONS).

Skin and subcutaneous tissue disorders:

Common: Pruritus

Investigations:

Common: Increased serum amylase, which may interfere with the diagnosis of pancreatitis. The elevated amylase is due to the formation of an enzyme-substrate complex of amylase and hydroxyethyl starch subject to slow elimination and must not be considered diagnostic of pancreatitis.

At high doses, the dilution effects may result in a corresponding dilution of blood components, such as coagulation factors and other plasma proteins, and a decrease in haematocrit.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Overdose with VOLULYTE can lead to overloading of the circulatory system (e.g. pulmonary oedema). In this case, the infusion should be stopped immediately and if necessary, a diuretic should be administered.

IDENTIFICATION

A clear to slightly opalescent solution, colourless to slightly yellow.

The solution is free from particles that can be observed on visual inspection.

PRESENTATION

VOLULYTE is packed in 500 ml polyolefin (freeflex®) bag. The bags are clear in colour. The freeflex® packaging system consists of a primary container (foil and tubing), administration port, and an overwrap with overwrap: Packed in 1's; 10's; 15's; 18's and 20's.

STORAGE INSTRUCTIONS

Store at or below 25 ºC. Do not freeze.

The product should be used immediately after opening.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

41/8.4/0211

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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