APPROVED PACKAGE INSERT

VOLUVEN®

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

VOLUVEN® solution for infusion

COMPOSITION

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 chloride	9,00 g

Electrolytes:

Na^+ 154 mmol, Cl^- 154 mmol

Theoretical osmolarity	308 mOsmol/ℓ
pH – value	4,0 – 5,5
Titratable acidity	< 1,0 mmol NaOH/ℓ

Inactive ingredients: Sodium hydroxide (for pH adjustment), hydrochloric acid (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.

HES 130/0,4 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 6 % HES 130/0,4 in 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 6 % HES 130/0,4 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 HES 130/0,4 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 plasma levels almost return to baseline after 24 hours.

Plasma clearance was 31,4 ml/min when 500 ml of 6 % HES 130/0,4 was administered, with an AUC of 14,3 mg/ml 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 HES 130/0,4 concentrations were 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**).

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

VOLUVEN, 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 VOLUVEN in:

- patients with known hypersensitivity to hydroxyethyl starch
- 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
- 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 or severe hyperchloraemia

WARNINGS AND SPECIAL PRECAUTIONS

- Caution is advised with the use of VOLUVEN in organ transplant patients.

- VOLUVEN 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 VOLUVEN should not exceed 24 hours.
- Generally, sufficient fluid should be administered in order to avoid dehydration.

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 VOLUVEN. If a hypersensitivity reaction occurs, administration of VOLUVEN 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 VOLUVEN 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 VOLUVEN.

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 VOLUVEN 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

Particular care must be taken in patients with electrolyte abnormalities.

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.

Monitor liver function in patients receiving VOLUVEN.

Effects on ability to drive and use machines

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

INTERACTIONS

No interactions with other medicines or nutritional products are known to date.

Interference with laboratory tests:

Elevated serum amylase levels may be observed following administration of the product and 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 VOLUVEN during labour or delivery is unknown with the exception of caesarean section.

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

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

DOSAGE AND DIRECTIONS FOR USE

- VOLUVEN 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.
- VOLUVEN is administered by intravenous infusion only.
- 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 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 duration of treatment with VOLUVEN should not exceed 24 hours.

Paediatric dose:

VOLUVEN 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**).

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

Instructions for use/handling

For single use only.

To be used immediately after the bag is opened.

Do not use VOLUVEN 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 (**free***flex*) and PVC 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), very rare (<1/10 000), frequency not known (cannot be estimated from the available data).

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 VOLUVEN 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 dosages the dilution effects may result in a corresponding dilution of blood components such as coagulation factors and other plasma proteins and a decrease of haematocrit.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Overdose with VOLUVEN 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, free from visible particles.

PRESENTATION

Free*flex*® bags (polyolefin bags):

With overwrap 20 x 250 ml; 15 x 500 ml

Without overwrap 40 x 250 ml; 20 x 500 ml

PVC bags: 250 ml and 500 ml bags with overwrap

STORAGE INSTRUCTIONS

Store at or below 25 °C. Do not freeze.

The product should be used immediately after opening.

KEEP THIS MEDICINE OUT OF SIGHT AND REACH OF CHILDREN.

REGISTRATION NUMBER

34/8.4/0417

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

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