SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion

Nirhes – 130 (6%)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each100 ml contains

Hydroxyethyl Starch (130/0.4)	6.00 gm
Sodium Choride	0.9 gm
Activated Charcoal	0.025 gm
Water for Injections	q.s.

3. PHARMACEUTICAL FORM

Intravenous Infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion is indicated for the treatment and prophylaxis of hypovolemia in adults and children. It is not a substitute for red blood cells or coagulation factors in plasma.

4.2 Posology and method of administration

Posology

Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion is administered by intravenous infusion only. The daily dose and rate of infusion depend on the patient's blood loss, on the maintenance or restoration of hemodynamic and on the hemodilution (dilution effect). Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion can be administered repetitively over several days.

The initial 10 to 20 mL should be infused slowly, keeping the patient under close observation due to possible anaphylactoid reactions.

Adult Dose

Up to 50 mL of Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion per kg of body weight per day (equivalent to 3g hydroxyethyl starch and 7.7 mEq sodium per kg of body weight). This dose is equivalent to 3500 mL of Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion for a 70 kg patient.

Paediatric Dose

The dosage in children should be adapted to the individual patient colloid needs, taking into account the disease state, as well as the hemodynamic and hydration status.

In 41 new born to infants (< 2 years), a mean dose of 16 ± 9 mL/kg was administered. In 31 children from 2 to 12 years of age a mean dose of 36 ± 11 mL/kg was administered. The dose in adolescents > 12 is the same as the adult dose.

4.3 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 (RRT).

Do not use HES products, in patients with severe liver disease.

Do not use HES products, in patients with known hypersensitivity to hydroxyethyl starch

Do not use HES products in clinical conditions with volume overload.

Do not use HES products in patients with pre-existing coagulation or bleeding disorders.

Do not use HES products in patients with renal failure with oliguria or anuria not related to hypovolemia.

Do not use HES products in patients receiving dialysis treatment.

Do not use HES products in patients with severe hypernatremia or severe hyperchloremia.

Do not use HES products in patients with intracranial bleeding.

4.4 Special warnings and precautions for use

Anaphylactoid Reactions

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

Renal Dysfunction

Avoid use in patients with pre-existing renal dysfunction.

Discontinue use of Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion 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 administration of HES products.

Coagulopathy

Monitor the coagulation status of patients undergoing open heart surgery in association with cardiopulmonary bypass as excess bleeding has been reported with HES solutions in this population. Discontinue use of Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion at the first sign of coagulopathy.

Fluid Equilibrium

Avoid fluid overload; adjust dosage in patients with cardiac or renal dysfunction. Fluid status and rate of infusion should be assessed regularly during treatment, especially in patients with cardiac insufficiency or severe kidney dysfunction.

In cases of severe dehydration, a crystalloid solution should be given first. Generally, sufficient fluid should be administered in order to avoid dehydration.

Monitoring: Laboratory Tests

Clinical evaluation and periodic laboratory determinations are necessary to monitor fluid balance, serum electrolyte concentrations, kidney function, acid-base balance, and coagulation parameters during prolonged parenteral therapy or whenever the patient's condition warrants such evaluation. Monitor liver function in patients receiving HES products.

Interference with Laboratory Tests

Elevated serum amylase levels may be observed temporarily following administration of the product and can interfere with the diagnosis of pancreatitis.

At high dosages the dilutional effects may result in decreased levels of coagulation factors and other plasma proteins and a decrease in haematocrit.

4.5 Interaction with other medicinal products and other forms of interaction

No studies have been conducted.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy Category C. Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion has been shown to cause embryocidal or other adverse effects in rats and rabbits when given in doses 1.7 times the human dose.

The type of hydroxyethyl starch present in Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion had no teratogen properties in rats or rabbits. At 5 g/kg of body

weight per day, administered as a bolus injection, fatal retardations and embryo lethal effects were observed in rats and rabbits, respectively. In rats, a bolus injection of this dose during pregnancy and lactation reduced body weight of offspring and induced developmental delays. All adverse effects were seen exclusively at maternal toxic doses due to fluid overload.

Fertility studies on directly exposed animals have not been conducted.

There are no adequate and well-controlled studies in pregnant women. Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

Information on the use of Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion during labor or delivery is unknown. Use if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion is administered to a nursing woman.

Pediatric Use

In one trial, newborns and infants < 2 years of age undergoing elective surgery were randomized to receive Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion (N=41) or 5% albumin (N=41). The mean dose of Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion administered was 16 ± 9 mL/kg.7

In an additional trial, children from 2 - 12 years of age undergoing cardiac surgery were randomized to receive Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion (N=31) or 5% albumin (N=30). The mean dose administered was 36 ± 11 mL/kg.

Use of Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion in adolescents > 12 years is supported by evidence from adequate and well-controlled studies of Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion in adults.

Dosage in children should be adapted to individual patient colloid needs, taking into account underlying disease, hemodynamics and hydration status.

Studies conducted in children have not been of sufficient size or follow-up duration to assess the risks of renal injury and mortality in this patient population.

Geriatric Use

Of the total number of subjects in clinical studies of Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion (N=471), 32% were ≥ 65 years old while 7% were ≥ 75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified

differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment

Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion is mainly excreted by the kidneys, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Volume status, infusion rate, and urine output should be closely monitored. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection.

4.7 Effects on ability to drive and use machines

There is no information on the effects of Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion on the ability to operate an automobile or other heavy machinery.

4.8 Undesirable effects

Serious adverse reactions reported in clinical trials include increased mortality and increased use of RRT in critically ill subjects, including subjects with sepsis.

The most common adverse reactions after administration of Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion occurring in more than 1% of patients are: pruritus (itching; ≥1% to <10%), elevation of serum amylase (≥1% to <10%; interference with the diagnosis of pancreatitis), and dilutional effects that may result in decreased levels of coagulation factors and other plasma proteins and in a decrease of hematocrit (≥1% to <10%).

Anaphylactoid reactions occur rarely in <0.1% after administration of hydroxyethyl starch solutions. Disturbances of blood coagulation beyond dilution effects can occur rarely in <0.1% depending on the dosage with the administration of hydroxyethyl starch solutions.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: “Blood substitutes and plasma protein fractions (Plasma volume expander)” ATC code: “B05AA07”.

Mechanism of Action

Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion contains hydroxyethyl starch in a colloidal solution which expands plasma volume when administered intravenously. This effect depends on the mean molecular weight (130,000 daltons; range 110,000 – 150,000 daltons), the molar substitution by hydroxyethyl groups (0.4; range 0.38 – 0.45) on glucose units of the starch, the pattern of hydroxyethyl substitution (C2/C6 ratio) of approximately 9:1, and the concentration (6%), as well as the dosage and infusion rate.

Hydroxyethyl starch is a derivative of thin boiling waxy corn starch, which mainly consists of a glucose polymer (amylopectin) pre-dominantly composed of α-1-4-connected glucose units with several α-1-6-branches. Substitution of hydroxyethyl groups on the glucose units of the polymer reduces the normal degradation of amylopectin by α-amylase in the body. The low molar substitution (0.4) is the main pharmacological determinant for the beneficial effects of Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion on pharmacokinetics, intravascular volume and hemodilution. To describe the molecular weight and molar substitution characteristics of the hydroxyethyl starch in Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion, the compound is designated as hydroxyethyl starch 130/0.4.

After isovolemic exchange of blood with 500 mL of Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion in healthy volunteers, blood volume is maintained for at least 6 hours.

5.2 Pharmacokinetic properties

The pharmacokinetic profile of hydroxyethyl starch is complex and largely dependent on its molar substitution as well as its molecular weight.8 When administered intravenously, molecules smaller than the renal threshold (60,000-70,000 daltons) are readily and rapidly excreted in the urine, while molecules with higher molecular weights are metabolized by plasma α-amylase prior to excretion via the renal route.

The mean in vivo molecular weight of Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion in plasma is 70,000 – 80,000 daltons immediately following infusion and remains above the renal threshold throughout the treatment period.

Following intravenous administration of 500 mL Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion to healthy volunteers, plasma levels of Hydroxyethyl Starch

(130/0.4) (6%w/v) Solution for Intravenous Infusion remain at 75% of peak concentration at 30 minutes post-infusion and decrease to 14% at 6 hours post-infusion. Plasma levels of Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion return to baseline levels 24 hours following infusion. Plasma clearance, volume of distribution, and elimination half-life of Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion in healthy volunteers following IV administration of 500 mL were 31.4 mL/min, 5.9 liters, and 12 hours, respectively. Approximately 62% of Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion was excreted as hydroxyethyl starch molecules in urine within 72 hours.

The pharmacokinetics of Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion are similar following single and multiple dose administration. No significant plasma accumulation occurred after daily administration of 500 mL of a 10% solution containing hydroxyethyl starch 130/0.4 over a period of 10 days. Approximately 70% of Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion was excreted as hydroxyethyl starch molecules in urine within 72 hours.

Renal Impairment:

Following a single intravenous administration of Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion (500 mL) in subjects with varying degrees of renal dysfunction, the AUC and clearance of Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion increased by 73% and decreased by 42% in subjects, respectively, with creatinine clearance < 50 mL/min as compared to subjects with creatinine clearance > 50 mL/min. However, terminal half-life and peak hydroxyethyl starch concentration were not affected by renal impairment. Plasma levels of Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion returned to baseline levels 24 hours following infusion. Approximately 59 % and 51 % of Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion were excreted as hydroxyethyl starch molecules in urine within 72 hours in subjects with creatinine clearance ≥30 mL/min and <30 mL/min, respectively.

There are no data available on the use of Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion in subjects undergoing haemodialysis.

Pharmacokinetic data in patients with hepatic insufficiency or in paediatric or geriatric patients are not available. Effects of gender or race on the pharmacokinetics of Hydroxyethyl Starch (130/0.4) (6%w/v) Solution for Intravenous Infusion have not been studied.

5.3 Preclinical safety data

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride

Activated charcoal

Water for Injections

6.2 Incompatibilities

6.3 Shelf life

36 Months from the date of manufacture

6.4 Special precautions for storage

Store below 30oC. Do not freeze. Protect from light.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

500 ml Non-PVC Plastic bag with spike port and an extra medication port.

6.6 Special precautions for disposal <and other handling>

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

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