For the use of Registered Medical Practitioner or a hospital or a laboratory only

NIRHES-200 (3%)™*

Hydroxyethyl Starch (200/0.5) (3% w/v) Solution for IV Infusion

NIRHES-200 (6%)™*

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1. **Do not use HES solutions in critically ill adult patients including those with sepsis, and those admitted to the ICU as it increases the risk of Mortality.**
2. **Avoid use in patients with pre-existing renal dysfunction.**
3. **Discontinue use of HES at the first sign of renal injury.**
4. **Need for renal replacement therapy has been reported up to 90 days after HES administration. Continue to monitor renal function for at least 90 days in all patients.**
5. **Avoid use in patients undergoing open heart surgery in association with cardiopulmonary bypass due to excess bleeding.**
6. **Discontinue use of HES at the first sign of coagulopathy.**

DESCRIPTION :

Hydroxyethyl starch (200/0.5) is a synthetic colloid for use in plasma volume replacement. The chemical name of hydroxyethyl starch is poly (O-2-hydroxyethyl) starch.

COMPOSITION :

Each 100 mL contains	**NIRHES-200 (3 %)™***	**NIRHES-200 (6 %)™***
Hydroxyethyl Starch (200/0.5)	Gms	Gms
Sodium Chloride IP	0.9 gms	0.9 gms
Water for Injections IP	q. s.	q. s.

CLINICAL PHARMACOLOGY :

PHARMACODYNAMICS :

The plasma expansion effects of the Hydroxyethyl starch (HES 200/0.5) are determined by its mean molecular weight, the molar substitution by hydroxyethyl groups on glucose units of the starch, the pattern of hydroxyethyl substitution (C2/C6 ratio), and the concentration as well as the dosage and infusion rate.

Hydroxyethyl starch is manufactured from amylopectin and is characterized by molecular weight and degree of substitution. The average molecular weight is approximately 200,000 Dalton, and the degree of substitution is approximately 0.5, i.e., approximately 5 hydroxyethyl groups are present in 10

glucose units of the amylopectin skeleton. The main chain in HES (poly-(O-2-hydroxyethyl) starch) is made up of alpha 1,4-linked glucose units and branched via alpha 1,6 bonds. On its close structural relationship to glycogen a high somatic tolerance and only a low risk of anaphylactoid reactions may be anticipated for Hydroxyethyl starch.

Hydroxyethyl starch is characterized by the high stability of the solution and does not flocculate in the event of temperature fluctuation.

PHARMACOKINETICS :

Hydroxyethyl starch has the colloidal properties.

Following the infusion of Hydroxyethyl starch (HES 200/0.5), There is an increase of plasma volume equivalent to approximately 140% of the volume infused. Within 340 minutes the increase in plasma volume drops to 50% of the infused volume.

Thus the expansion brings about an improvement in circulation and microcirculation over a period of approximately 4 hours. Hydroxyethyl starch is degraded continuously by serum amylase and eliminated approximately 4 hours. Hydroxyethyl starch is degraded continuously by serum amylase and eliminated predominantly via the kidneys. Whereby approximately 70% appears in the urine within 24 hours at which point only 2% can still be detected in the plasma.

Hydroxyethyl starch (HES 200/0.5) has a plasma half-life of approximately 4 hours. Small amounts are temporarily stored in the tissues. Hydroxyethyl starch (HES 200/0.5) can be eliminated by diafiltration, but not by dialysis.

The intravascular half-life and retention time, respectively, are correlated with the severity of renal insufficiency.

After 30 minutes, sodium chloride is distributed over the whole extracellular space. Sodium chloride is mainly eliminated renally, small amounts are excreted transcutaneously.

THERAPEUTIC INDICATIONS :

Hydroxyethyl starch (HES 200/0.5) is indicated for

- prophylaxis of hypovolaemia (volume deficiency)
- shock (volume replacement therapy)
- Surgery (haemorrhagic shock)
- Trauma (traumatic shock, injuries)
- Infections (septic shock)
- Burns (burn shock)

It is not a substitute for red blood cells or coagulation factors in plasma.

DOSAGE & ADMINISTRATION :

In the light of possible anaphylactoid reaction the initial 10-20 ml Hydroxyethyl starch (200/0.5) is to be infused slowly, keeping the patient under close observation.

Special caution is recommended in the case of patients with disturbed coagulation, heart failure and pulmonary oedema, renal failure and chronic hepatic diseases.

Administration as intravenous infusion: The daily dose and rate of infusion are to be determined

according to blood loss and haemoconcentration.
The therapeutic limit is based on the haemodilution effects.
Duration of administration: there is no pharmacological or clinical evidence to give cause for concern with regard to a repeated administration. The duration and extent of the treatment are to be determined according to the duration and extent of the hypovolaemia.

2) Recommended dosage for haemodilution therapy –
Daily dose: a) 500 ml/day (medium dose).
b) 2 × 500 ml in 8-12 hours (125-83 ml/hour).

If administration by pressure infusion, all air should be withdrawn or expeller from the bag through the medication prior to infusion.
Haemodilution therapy with HES 200/0.5 is recommended daily over a period of 7-10 days. Whereb administration may be performed hypervolaemic (without bloodletting) or isovolaemic (with blood-letting).

Preparation for Administration (Use aseptic technique):
1. Close flow control clamp of administration set.
2. Insert spike of infusion set into infusion port
3. Suspend container from hanger.
4. Follow manufacturer's recommended procedures for the administration
5. Discontinue administration and notify physician immediately if patient exhibits signs of adverse reactions.

CONTRAINDICATIONS:
Hydroxyethyl starch (HES 200/0.5) is contraindicated in
- Bleeding (haemorrhagic) disorders.
- Congestive heart failure (cardiac insufficiency).
- Renal failure with oliguria or anuria not related to hypovolemia.
- Known hypersensitivity to hydroxyethyl starch.

In the event of fibrinogen deficiency Hydroxyethyl starch should be administered only in potentially fatal emergencies until such time as blood is on hand for substitution.
Hydroxyethyl starch should not be used during pregnancy.

SPECIAL PRECAUTIONS & WARNINGS :
WARNINGS:
General: Administration of large volumes of Hydroxyethyl starch (HES 200/0.5) will decrease hemoglobin concentration and dilute plasma proteins excessively.

Administration should be kept below the recommended dose of 2000 ml in 24 hours.
Large volumes of Hydroxyethyl starch (HES 200/0.5) will alter the coagulation mechanisms without triggering clinical hemorrhage.

The physician should also be alert to the possibility of transient prolongation of bleeding time.

Pregnancy: There are no adequate and well-controlled clinical studies established using HES 200/0.5 in pregnant women. HES 200/0.5 should not be used during pregnancy unless potential benefits justify the potential risk to the foetus.

Lactation: It is not known whether HES 200/0.5 is excreted in human milk. caution should be exercised when HES 200/0.5 is administered to a nursing mother.

Children: The safety and efficacy of HES 200/0.5 in children have not been established.

PRECAUTIONS:

In the event of intolerance reactions, the infusion is to be discontinued immediately and the standard emergency measures have to be initiated.

a) In case of subject complaints (dorsalgia, nausea, etc.), discontinuation of infusion.

b) In case of allergic skin reactions, administration of antihistamines, discontinuation of infusion.

c) In the event of a rise in heart rate and fall in systolic blood pressure to below 90 mmHg, administration of corticosteroids I.V. (e.g., 100 mg prednisolone), discontinuation of infusion.

d) In case of difficult of breathing and shock, administration of high dose corticosteroids (e.g., 1 gram prednisolone), Oxygen, adrenaline (drip) and volume replenishment, changing the volume substitute, discontinuation of infusion.

e) In case of respiratory or cardiac arrest, resuscitating & discontinuation of infusion.

f) Cardiovascular, circulatory overload and pulmonary oedema.

g) Other: vomiting, peripheral oedema of the lower extremities, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches and muscle pains.

Special care should be taken in patients who have impaired renal clearance since this is the principal route by which HES 200/0.5 is eliminated.

Special care should be taken before administering HES 200/0.5 to patients with a history of liver disease.

Caution should be exercised when administering HES 200/0.5 to patients allergic to corn because such patients can also be allergic to HES 200/0.5.

DRUG INTERACTIONS:

If a mixture with other drugs is necessary, hygienic injection, complete mixing and compatibility has to be taken care of. The results of compatibility tests are provided on request.

Use in conjunction with heparin may extend bleeding time

The concentration of serum amylase can rise during administration of hydroxyethyl starch and can interfere with the diagnosis of pancreatitis.

ADVERSE REACTIONS:

Coagulation disorders or hemorrhage may occur in association with the use of HES 200/0.5 as a plasma volume expander.

Headache, diarrhea, nausea, weakness, temporary weight gain, insomnia, fatigue, fever, oedema, paresthesia, acne, malaise, shakiness, dizziness, chest pain, chills, nasal congestion, anxiety and increased heart rate may occur after administration of HES 200/0.5.

Anaphylactoid reactions/ Hypersensitivity may occur (wheezing, urticaria and hypotension) with HES

200/0.5

OVERDOSE:
The treatment of overdosage would be essentially symptomatic & supportive.
Overdosage may cause hypernatraemia. In this case, fluid compensation, and induction of forced diuresis in hypervolaemic conditions have to be initiated.

SPECIAL INSTRUCTIONS:
Caution: Before administering to patient:

1. Check that the solution is clear.
2. Inspect the intact unit for signs of obvious damage. If present, the unit should not be used.

STORAGE:
Store below 30° C. Do not freeze. Protect from light.

PRESENTATION:
500 mL plastic bottle.

ACULIFE®
Manufactured in India by:
Aculife Healthcare Pvt. Ltd.
Sachana, Gujarat 382150, India.
* TM owners-Nirma Ltd.