RESTORVOL 6%, solution for infusion
500 ml in overwrapped ECOBAG (polypropylene/PE/ polyester), pack of 20
(CIP: 383 844-2)

Applicant: B BRAUN MEDICAL SAS
Hydroxyethyl starch
Sodium chloride
ATC code: B05AA07
Date of Marketing Authorisation: 15 February 2008 (national registration procedure)
Reason for request: Inclusion on the list of medicines approved for use by hospitals.
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Hydroxyethyl starch (HEA 130/0.42)
Sodium chloride
Sodium 154 mmol/l
Chlorides 154 mmol/l
Theoretical Osmolarity: 309 mOsm/l
Molar substitution ratio (MSR): 0.42
Mean Molecular Weight 130,000 Da
Acid titration: <1.0 mmol/l
pH: 4.0-6.5

1.2. Indications

“Prophylaxis and treatment of hypovolaemia, in particular when repeated volume replacement is required”.

1.3. Dosage

**Dosage**
The dosage depends on the degree of hypovolaemia and the patient’s age, body weight and haemodynamic status.

Maximum daily dosage:
On the first day of treatment, the dose of Restorvol 6% administered should not exceed 33 ml/kg/24 hours, i.e. 2,500 ml of solution for a patient of 75 kg. The dose is reduced to 20 ml/kg/24 hours on the following two days.
Restorvol 6% may be administered repeatedly for several days, as required.
The duration of treatment depends on the duration and severity of the hypovolaemia, the patient’s haemodynamic status and the degree of haemodilution.

Clinical experience with a maximum daily dosage of 50 ml/kg is currently limited in the case of administration over prolonged periods.
The efficacy and safety of Restorvol 6% have not been studied in children.

**Method of administration**
Strict intravenous route, by infusion.

Blood pressure and where necessary haemodynamic status should be monitored to prevent any risk of vascular overload.
2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)
B : blood and haematopoietic organs
B05 : blood substitutes and infusion solutions
B05A : blood and derivatives
B05AA : blood substitutes and plasma protein fractions
B05AA07 : hydroxyethyl starch.

2.2. Medicines in the same therapeutic category
Other hydroxyethyl starches (HES):
- VOLUVEN 6%\(^1\) (HEA 130/0.4)
- HEAFUSINE 6% and 10% (HEA 200/0.5)
- HYPERHES (HEA 200/0.5)
- PENTASTARCH 6% (HEA 200/0.5)
- PLASMOHES 6% and 10% (HEA 200/0.5)

2.3. Medicines with a similar therapeutic aim
Other plasma volume expanders:
- Crystalloids (0.9% SODIUM CHLORIDE, RINGER, RINGER LACTATE)
- Colloids:
  - Natural colloids: albumin (BAXTER HUMAN ALBUMIN, OCTALBINE, VIALEBEX).
  - Synthetic colloids including, in addition to other hydroxyethyl starches:
    - modified fluid gelatins (GELOFUSINE, HAEMACCEL, PLASMIION)
    - dextrans (DEXTRAN SORBITOL, HEMODEX, PLASMACAIR, RESCUEFLOW, RHEOMACRODEX).

\(^1\) Hydroxyethyl starch of molecular weight 130,000 daltons with a molar substitution of between 0.38 and 0.45. Its concentration is 6%.
3.1. Efficacy

A clinical study compared RESTORVOL 6% with an Hydroxyethyl starch (HES) 200/0.5 in gynaecological surgery\(^2\). No clinical study has compared RESTORVOL with VOLUMEN, the HES with the closest composition.

**NB:**

- A double-blind randomised controlled study performed in 40 coronary surgery patients\(^3\) compared the haemodynamic parameters of RESTORVOL and an HES 200/0.5. The data were published in abstract form with no quantitative result. No comment is therefore made about the results of this study.

- One study compared the volume expansion efficacy and safety of a HES 130/0.42 (RESTORVOL 6%) with those of a HEA 200/0.5 in patients undergoing major urological surgery. No difference was observed between the administered volumes of RESTORVOL and HES 200/0.5. As the results of this study were provided in abstract form\(^4\), it won’t be commented.

### Summary of the study comparing RESTORVOL 6% 130/0.4 with a 6% HES 200/0.5 in gynaecological surgery\(^2\)

**Purpose:** to compare the effects of RESTORVOL 6% (130/0.4) and a 6% HES 200/0.5 on the maintenance of haemodynamic parameters in women undergoing major gynaecological surgery.

**Method:** This was a randomised double-blind comparative study versus HES 200/0.5, in 60 women undergoing gynaecological surgery and liable to receive a plasma volume expander during the perioperative period.

The outcome variable was the volume of HES required to maintain a satisfactory haemodynamic status between the induction of anaesthesia and 6 hours after surgery. The equivalence between the mean volumes of the two HES administered was tested. The two volume expanders were considered equivalent if the difference in mean volumes \(\text{Vol.}_{\text{RESTORVOL}} - \text{Vol.}_{\text{STANDARD HES}}\) was lower than 500 ml.

Secondary endpoints were the haemodynamic, haematological and clotting parameters, blood or blood substitute requirements and blood and fluid losses.

**Results:**

Between anaesthesia induction and 6 hours after surgery, the mean volume of HES administered was 1,224 ± 544 ml in the RESTORVOL group and 1,389 ± 610 ml in the HES 200/0.5 group. The equivalence of the two HES solutions for the criterion “volume of replacement fluid administered” was established according to the margin of equivalence fixed for this study.

There was no statistically significant difference between the two HES for the haemodynamic parameters, which were maintained during the study, and for the blood transfusion or blood substitute requirements.

No difference was observed for the other criteria.

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\(^2\) Sander O. and al; Equivalence of hydroxyethyl starch HES 130/0.4 and HES 200/0.5 for perioperative volume replacement in major gynaecological surgery. Acta Anaesthesiologica Scand 2003; 47: 1151-1158.


\(^4\) Heinze H et al. Comparison of perioperative volume requirements of HES 130/0.42 and HES 200/0.5 in major urological surgery. European Journal of Anaesthesiology; 2005; 22 (Suppl 34, abstract): 78.
3.2. **Adverse effects**

According to the SPC data and those presented by the laboratory, the safety profile of 6% RESTORVOL is the same as that of other HES. The expected adverse reactions with HES are in particular a reduction in the haematocrit due to haemodilution, coagulation disorders such as Von Willebrand disease, hepatobiliary disorders and rarely, pruritis after repeated administration of high doses of HES.

According to the SPC, the use of a HES with a higher molecular weight (> 200,000 Da) and molar substitution rate (> 0.62) induced renal toxicity in patients with severe sepsis.

3.3. **Conclusion**

6% RESTORVOL (HES 130/0, 42/6: 1) and a standard HES (200/0.5) were shown to have an equivalent volume expansion efficacy (infused volumes and haemodynamic parameters) in a controlled clinical study carried out in 60 women undergoing gynaecological surgery.

Because of its physicochemical characteristics (molecular weight, molar substitution ratio and C2/C6 ratio), RESTORVOL 6% could theoretically reduce the toxicity of these products and, in particular their renal toxicity. However, the available data showed no difference in safety assessed from adverse reactions to RESTORVOL and a standard HES (200/0.5).

No clinical study has directly compared the blood volume expansion efficacy and/or safety of RESTORVOL 6% with those of VOLUMEN (HES with the closest composition but with a C2/C6 ratio of 9:1).

The tolerance profile of RESTORVOL 6% was similar to that of other HES.
4.1. Actual benefit

RESTORVOL 6% is used in life-threatening clinical situations (hypovolaemic shock). This proprietary product is intended for curative and preventive treatment. It is used for first-line therapy. There are alternative therapies: other HES, other plasma volume expanders.

**Public Health Benefit:**
There are many clinical conditions in which a plasma volume expander may be required though these are not easily quantifiable. The public health burden corresponding to these situations cannot therefore be estimated.

The therapeutic need is already covered by existing blood volume expanders.

According to the available data, RESTORVOL is not expected to have any additional impact on morbidity and mortality compared to other volume expanders. Consequently, RESTORVOL is not expected to have an impact on public health.

The efficacy/adverse effects ratio of RESTORVOL 6% is high.

The actual benefit of RESTORVOL 6% is substantial.

4.2. Improvement in actual benefit

RESTORVOL 6% does not improve actual benefit compared to other medicinal products in this class (HES).

4.3. Therapeutic use

The purpose of plasma volume expanders is to correct an absolute or relative blood volume deficiency. There are two main categories of plasma expanders: crystalloids which act through their osmolality and colloids which have a mainly oncotic effect.

“All intravascular volume expanders have an equivalent efficacy, provided they are administered at doses which take into account their diffusion space (which depends on their osmolality and their oncotic capacity).

The choice between a colloid and a crystalloid depends in particular on the clinical setting (haemorrhagic shock, hypovolaemia due to dehydration, septic or anaphylactic shock, drug poisoning for example)\(^5\).

“Colloids, have the advantage that they require a smaller volume and are more rapidly effective than crystalloids. Among colloids, it is recommended to use HES which have fewer adverse reactions than gelatins which are of plant origin. HES have a high plasma volume expansion capacity and a prolonged efficacy\(^5\).

“Low molecular weight hydroxyethyl starches (HEA) interfere less with coagulation values than high molecular weight HES though the maximum recommended dose is 33 ml/kg/day on day 1 and 20 to 33 ml/kg on the following days\(^5\).

Among HES, RESTORVOL provides an additional means of therapy for the prescriber.

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4.4. Target Population

There are many (unpredictable) clinical settings requiring the prescription of a plasma volume expander. There is no data to estimate the target population of this product in the hospital.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the indication and at the dosage of the MA.