



HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

13 May 2009

PLASMAVOLUME 6%, solution for infusion
500 mL in a bag (polypropylene), box of 10 (CIP: 390 526-2)

Applicant: BAXTER SAS

Hydroxyethyl starch 130/0.42 in a Ringer's acetate solution

ATC code: B05AA07

Date of Marketing Authorisation: 10 December 2008

Mutual recognition registration procedure (Rapporteur country: Germany)

Reason for request: Inclusion on list of products for hospital use.

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active substance

Colloidal hydroxyethyl starch	(HES 130/0.42)
Molar substitution:	0.42
Mean molecular weight	130,000 Daltons

Ringer's acetate solution

(balanced acid-base electrolyte component, crystalloid electrolyte solution)

Sodium	130.0	mmol/L
Chloride	112.0	mmol/L
Acetate	27.2	mmol/L
Potassium	5.36	mmol/L
Calcium	0.912	mmol/L
Magnesium	0.984	mmol/L

Excipient: Water For Injection; HCl (for pH adjustment)

pH: 5.0-7.0

Theoretical osmolarity: 277 mOsm/L

Iso-oncotic solution

1.2. Novel aspects

PLASMAVOLUME 6% combines a balanced acid-base Ringer's acetate solution and a colloidal hydroxyethyl starch.

1.3. Indications

"Treatment for imminent or manifest hypovolaemia and shock"

1.4. Dosage

The daily dose and infusion rate depend on the extent of blood loss, maintenance or restoration of haemodynamic parameters, and the level of haemodilution. The first 10–20 ml should be infused slowly and with careful patient monitoring so that possible anaphylactoid reactions can be detected as early as possible. The maximum infusion rate depends on the clinical situation. Patients in acute hypovolaemic shock may be administered up to 20 ml per kg body weight per hour (equivalent to 0.33 ml/kg body weight/min or 1.2 g hydroxyethyl starch per kg body weight per hour). In life-threatening situations 500 ml may be administered by pressure infusion.

The maximum daily dose is 50 ml PLASMAVOLUME 6% per kg body weight (equivalent to 3.0 g hydroxyethyl starch, 6.5 mmol sodium and 0.268 mmol potassium per kg body weight). This is equivalent to 3,500 ml PLASMAVOLUME 6% for a patient weighing 70 kg.

Method of administration and duration of therapy: intravenous infusion.

In life-threatening situations, 500 ml may be administered as a rapid infusion (under pressure). The infusion rate will usually be lower for selected peri-operative indications, in the case of burns and septic shock.

The duration of treatment will depend on the degree of hypovolaemia and the haemodynamic response.

Treatment of children

In children no clinical studies on PLASMAVOLUME 6% have been carried out and experience of use of HES 130/0.42 is only limited. However, some clinical studies have been carried out involving solutions containing HES. See the SPC.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

B:	blood and blood-forming organs
B05:	blood substitutes and perfusion solutions
B05A:	blood and related products
B05AA:	blood substitutes and plasma protein fractions
B05AA07:	hydroxyethylstarch

2.2. Medicines in the same therapeutic category

Other hydroxyethyl starches (HES):

- RESTORVOL 6% (HES 130/0.42)
- VOLUVEN 6%¹ (HES 130/0.4)

- HEAFUSINE 6% and 10% (HES 200/0.5)
- HYPERHES (HES 200/0.5)
- PENTASTARCH 6% (HES 200/0.5)
- PLASMOHES 6% and 10% (HES 200/0.5)

2.3. Medicines with a similar therapeutic aim

Other volume replacement solutions:

- Crystalloids (sodium chloride 0.9%, Ringer, Ringer's lactate)
- Colloids:
 - Natural colloids, albumin: BAXTER HUMAN ALBUMIN, OCTALBINE, VIALEBEX
 - Synthetic colloids, which include, apart from the other hydroxyethyl starches:
 - modified fluid gelatins: GELOFUSINE, HAEMACCEL, PLASMION
 - dextrans: DEXTRAN SORBITOL, HEMODEX, PLASMACAIR, RESCUEFLOW, RHEOMACRODEX.

¹ Hydroxyethyl starch with molecular weight of 130,000 Daltons with molar substitution of between 0.38 and 0.45. 6% concentration.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

PLASMAVOLUME 6% is distinctive in that it contains acetate and electrolytes in the infusion solution which, by making up for potential bicarbonate losses, prevents acidosis secondary to administration of HES 6% (130/0.42) in an isotonic NaCl solution.

Two comparative clinical studies have been done to attempt to assess the usefulness of such a strategy:

- the results of the first study will not be examined here, as the study was not comparative;
- the second study (phase III), which was randomised, compared the efficacy and tolerance of an infusion of HES 130/0.42 in an electrolyte solution containing Ringer's acetate (PLASMAVOLUME 6%) with an infusion of HES 130/0.42 in a NaCl 0.9% solution.

Results of the randomised comparative study²

This study involved 62 patients who were due to undergo abdominal or urological surgery. The following parameters were monitored: blood gases including acid-base balance, coagulation screen, FBC, blood loss, haemodynamic parameters, diuresis. At baseline, no significant difference in these parameters was observed between the two arms. Data were gathered at various points during the procedures.

No difference between the two arms was observed in terms of the following parameters:

	Ringer + HES 130/0.42 PLASMAVOLUME 6% 29 patients	HES 130/0.42 32 patients
Blood loss (mL)	1,156 ± 917	1,227 ± 691
Plasma substitutes (mL)	6,038 ± 1,863	6,317 ± 1,325
Diuresis (mL)	3,286 ± 1,232	3,450 ± 1,337

Base excess fell after the start of the procedure in both arms, but this reduction was greater in the control arm than in the arm receiving buffer substance ($p < 0.001$). There was no difference in blood pH between the two arms. Significant haemodilution (16-18%), which was assessed using haemoglobin and haematocrit measurements, was observed in both arms. Haematology parameters changed in similar ways in both arms over the period in question. Coagulation values remained close to normal levels in both arms (apart from a reduction in prothrombin ratio in the control arm during and after the procedure, $p < 0.001$).

Comments: the objective of this study was not clearly defined. The multiple endpoints, the repeated measurements of each parameter throughout the study, and the limited number of patients mean that it is not possible to draw conclusions as to the difference between the results in the two arms.

3.2. Adverse effects

According to the data in the SPC and those presented by the applicant, the safety profile of PLASMAVOLUME 6% does not appear to be different to that of other HES.

The expected adverse effects of HES include: reduction in haematocrit caused by haemodilution, haemostasis problems such as von Willebrand disease, and hepatobiliary disease; in rarer cases, itching can occur following repeated administration of high doses of HES.

² Kulla M., Weidhase R. et Lampl L. Hydroxyethyl starch 6% 130/0.42 in Ringer's acetate as part of a balanced volume replacement regimen in abdominal surgery. *Anäth Intensivmed* 2008; 49: 7-18.

3.3. Conclusion

In a single controlled clinical study, no difference in efficacy was shown in terms of volume expansion (volumes infused and haemodynamic parameters) between PLASMAVOLUME 6% (HES 130/0.42/6:1) and a standard HES solution (130/0.42) in 62 patients undergoing abdominal and urological surgery.

PLASMAVOLUME 6% has not been shown to provide an additional clinical benefit over and above that provided by other volume expanders.

The safety profile for PLASMAVOLUME 6% does not appear to differ from those of other types of HES.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The clinical situations in which PLASMAVOLUME 6% is required are likely to be life-threatening (hypovolaemic shock). This medicinal product is intended as curative and preventative therapy. This is a first-line therapy.

There are treatment alternatives: other types of HES, other volume replacement products.

Public health benefit:

There are multiple types of clinical situation in which a volume replacement solution is required, and these are difficult to quantify. For this reason, the public health burden represented by these situations cannot be estimated. The treatment need is already met by existing volume replacement products. Given the available data, PLASMAVOLUME is not expected to have any additional impact on morbidity and mortality in comparison with other volume replacement products.

As a result, PLASMAVOLUME is not expected to benefit public health.

The efficacy/adverse effects ratio of HES 130/0.42 in a Ringer's acetate solution is high.

The actual benefit provided by PLASMAVOLUME 6% is substantial.

4.2. Improvement in actual benefit (IAB)

PLASMAVOLUME 6% provides no improvement in actual benefit in comparison with other medicinal products of the same type (HES).

4.3. Therapeutic use

The aim of volume replacement is to correct a volume deficiency, whether absolute or relative. There are two main types of volume replacement product: crystalloids, the effects of which are linked to their osmolality, and colloids, the effects of which are related to their oncotic properties.

"All volume replacement products have the same level of efficacy, as long as they are administered at doses that take into account their diffusion distance (a function of their osmolality and oncotic properties).

The choice of a colloid or a crystalloid depends mainly on the clinical background (for example haemorrhagic shock, hypovolemia linked to dehydration, septic shock or anaphylaxis, drug intoxication)"³.

"Colloids have the advantage that a lower volume is needed, and act more quickly than crystalloids. When choosing a colloid, it is recommended that HES be used; these have fewer adverse effects than gelatins and are vegetable-based. HES have excellent volume expansion properties and are effective over long periods"⁵.

"Low molecular weight hydroxyethyl starches (HES) have less effect on haemostasis than high molecular weight HES; however, the maximum recommended dose is 33 mL/kg/day on the first day and 20-33 mL/kg on subsequent days"⁵.

"Buffer substances and correction of acidosis are only required in specific situations: excessive bicarbonate loss, metabolic acidosis associated with hyperkalaemia or in the context of intoxication with membrane-stabilising products.

Aside from pH correction, no buffer substance has been shown to be clinically effective in the treatment of metabolic acidosis."

³ Consensus conference of the French Language Intensive Care Society (SRLF) on choices of volume replacement products for the treatment of hypovolemia in adults; Guidelines of the French Anaesthesia and Intensive Care Society; ANAES, January 1997.

Among the various types of HES, PLASMAVOLUME 6% is an additional therapeutic tool for prescribers.

4.4. Target population

There are multiple clinical situations in which a volume replacement solution might be required. There are no data that indicate how large the target hospital population for this product might be.

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 indications and at the dosage in the Marketing Authorisation.