

**NOTIFICATION OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE  
2001/83/EC**  
**FAX NUMBER:000442075237051**

This notification is an official referral under Article 31 of Directive 2001/83/EC made by Germany:

Product name(s), if appropriate, Strength(s) and Pharmaceutical Form(s)	All HES containing solutions for infusion
Active Substance(s)	Hydroxyethyl Starch (HES)
Marketing Authorization Holder(s)	Various

Hydroxyethyl starch solutions are colloid solutions for intravenous therapy of hypovolaemia to obtain rapid and lasting circulatory stabilization. They include products with starch derived from potato or corn (waxy maize), starch with different molecular weights (200kD; 130kD), substitution ratios (the number of hydroxyethyl groups per glucose molecule) and at different concentrations. Hydroxyethyl starch solutions are primarily indicated for the treatment of hypovolaemia and hypovolaemic shock.

In the therapy of patients with hypovolaemia due to severe sepsis the mainstay of treatment is the application of intravenous fluids. Colloid solutions are used for volume substitution in these patients but there are limited data to support this practice and the use of HES in patients with severe sepsis and its routine use has recently been discouraged<sup>1</sup>.

In June 2012 the Scandinavian Starch for Severe Sepsis/Septic Shock (6S) Trial<sup>2</sup> to evaluate the effects of 6% HES 130/0.42 as compared with Ringer's acetate on the composite outcome of death or end-stage kidney failure in patients with severe sepsis has been published suggesting that patients with severe sepsis have an increased risk of death (Relative Risk, 1.17; 95% confidence interval [CI], 1.01 to 1.36; P=0.03) and were more likely to receive renal replacement therapy (Relative Risk, 1.35; 95% CI, 1.01 to 1.80; P=0.04) when treated with HES as compared to Ringer's acetate. There is also a trend for a higher rate of severe bleedings in the HES arm of the study. The study failed to show any improvement in survival for HES 130/0.42 treated patients with severe sepsis. The results of this trial point in the same direction as the results of the earlier VISEP study (10% HES 200/0.5 vs. Ringer's lactate)<sup>3</sup>.

Another large study, the Crystalloid Versus Hydroxyethyl Starch Trials (CHEST)<sup>4</sup> conducted in 7000 intensive care patients has recently been published. For the primary outcome death at day 90 there was no significant difference between the 6% HES (130/0.4) group and the saline group

<sup>1</sup> Reinhart K. et al., Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. *Intensive Care Med* 2012;38.

<sup>2</sup> A. Perner et al. Hydroxyethyl Starch 130/0.42 versus Ringer's Acetate in Severe Sepsis. *N Engl J Med* 2012; 367: 124-34

<sup>3</sup> Brunkhorst, F.M. et al., Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med*, 2008


<sup>4</sup> John A. Myburgh et al. Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care; *N Engl J Med* October 2012. DOI: 10.1056/NEJMoa1209759

(Relative Risk, 1.06; 95% CI, 0.96 to 1.18; P = 0.26). There was no difference in 90-day mortality in any of the predefined subgroups, including patients with sepsis. However, renal replacement therapy was significantly more frequent in the HES group than in the saline group (Relative Risk, 1.21; 95% CI, 1.00 to 1.45; P = 0.04).

In conclusion, two studies (VISEP and 6S) showed a higher risk of mortality in septic patients who were treated with HES and a higher risk of negative effects on renal function has been shown for all ICU (Intensive Care Unit) patients. Further review of the benefit risk balance for the use of HES containing medicinal products in critically ill/ICU patients including septic patients is therefore warranted.

In the light of the above DE considers that it is in the interest of the Community to refer HES containing solutions for infusions to the Pharmacovigilance Risk Assessment Committee and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC, as amended, on whether the balance of benefits and risks is positive in the management of hypovolemia and hypovolemic shock in critically ill/ICU patients and in particular in patients with sepsis and whether the Marketing Authorizations for solutions for infusions containing HES in the above mentioned indication should be maintained, varied, suspended or withdrawn.

A draft list of questions to be submitted to the MAHs is annexed.



Prof. Dr. Walter Schwerdtfeger

President of BfArM

Date 20. Nov. 2012

## ANNEX 1

**Draft** List of Questions to MAHs of Hydroxyethyl Starch (HES) containing medicinal products, solutions for infusion, authorized in the EU/EEA:

1. What marketing authorisations do you hold for medicinal products containing HES in the European Union/EEA (name, marketing authorisation number or EU procedure number, type of marketing authorisation, concentration/molecular weight/degree of substitution of HES, date of marketing authorisation, composition, indication, posology), and what were the sales figures over the past 5 years in each case for the single countries in the EU/EEA?\*
2. The benefit of HES for patients with sepsis should be discussed by the MAHs, compared to other colloid solutions and compared to crystalloid solutions.
3. The benefit in critically ill patients/ICU patients should be discussed by the MAHs compared to other colloid solutions and compared to crystalloid solutions.
4. Provide a full benefit risk assessment for your HES product including the results of both studies: "Hydroxyethyl Starch 130/0.42 versus Ringer's Acetate in severe sepsis trial (6S Study)" and the recently published Australian study, the "Crystalloid versus Hydroxyethyl Starch Trial (CHEST)".
5. To what extent is information on the risks of administration of HES already included in the product information regarding
  - a. patients with renal insufficiency?
  - b. patients with sepsis and renal insufficiency dependent on dialysis?
  - c. patients with sepsis, in particular with regard to potentially increased overall mortality?

Do you intend to add new information concerning these subjects? Please submit appropriate suggestions for minimizing risks and changes to the product information texts.\*

6. What is the impact on other indications of HES?

\* The question has already been answered by the MAHs with HES containing medicinal products (solution for infusion) authorized in DE in response to a request by BfArM on a national basis.