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Assessment report for solutions for infusion containing hydroxyethyl starch

Procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure number: EMEA/H/A-31/1348

Final Assessment Report as adopted by the PRAC with all information of a confidential nature deleted.



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1. Background information on the procedure

On 20 November 2012, Germany informed the European Medicines Agency, pursuant to Article 31 of Directive 2001/83/EC, of their consideration to review the benefit risk balance of HES solutions for infusion in the treatment and prophylaxis of hypovolemia and hypovolemic shock resulting from the evaluation of data relating to pharmacovigilance showing an increased risk of mortality and renal replacement therapy (RRT) in patients treated with HES.

2. Scientific discussion

Hydroxyethyl starch (HES) solutions for infusion include products with starch derived from potato or corn (waxy maize), with different molecular weights (mainly 130kD; 200kD) and substitution ratios (the number of hydroxyethyl groups per glucose molecule). More than 80% of patients treated with HES receive HES 130kD. HES containing solutions for infusion are authorised worldwide including all EU and EEA countries with the main indication for the treatment and prophylaxis of hypovolaemia and hypovolemic shock.

In the therapy of patients with hypovolemia 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.

Concerns with regards to HES were previously considered by the Pharmacovigilance Working Party in September 2008 on the basis of results of several studies, some of which showing an increased risk for renal RRT or acute renal failure. Published studies (6S¹, VISEP²) including a recent one (6S) provided further data supporting an increased risk of mortality at day 90 and RRT in patients with sepsis. Furthermore, the higher risk for RRT was shown in another recently published large clinical trial for all intensive care unit (ICU) patients (CHEST³) supporting the results of the 6S study. Mortality difference was not confirmed, however, the study enrolled a broad mixture of patients with on average lower baseline mortality risk admitted to intensive care units. Although some limitations of the studies were raised, the data which were collected from these large randomised clinical trials were considered solid enough to indicate a potential harm associated with HES.

In view of the above, the PRAC was requested to assess the benefit risk balance of HES containing medicinal products for solutions for infusion in the treatment and prophylaxis of hypovolaemia and hypovolemic shock.

2.1. Clinical aspects

Fluid resuscitation and blood volume substitution are fundamental interventions in many different clinical situations. The need to substitute fluid or blood volume may result from an actual loss of plasma or blood volume, but also from the relative hypovolemia induced by pathological vasodilation, such as in sepsis. A direct loss of blood volume may occur as a consequence of direct injury, such as bleeding during surgery or in trauma, but it may also be a result of an altered capillary permeability with consequent extravasation of plasma volume. This latter situation is encountered in situations with massive inflammatory activation, such as in sepsis and burn injury.

¹ Perner A, Haase N, Guttormsen AB *et al.* Hydroxyethyl starch 130/0.42 versus ringer's acetate in severe sepsis. *N Engl J Med* 2012 Jul 12; 367(2): 124-34

² Brunkhorst FM, Engel C, Bloos F *et al.* Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis. *N Engl J Med* 2008; 358(2): 125-39

³ Myburgh J, Finder S, Bellomo R *et al.* Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012; 367: 1901-11

When crystalloids (saline or balanced salt solutions) are used for blood volume replacement they are distributed across the entire extracellular space, as governed by capillary permeability and the Starling equilibrium. Consequently, in theory, approximately $\frac{3}{4}$ of a given crystalloid volume is redistributed to the extracellular space, leaving only $\frac{1}{4}$ as effective blood volume replacement. The expansion of the extracellular space may be seen as an unwanted side effect.

This provides the rationale for blood volume replacement with colloid solutions. Colloids are molecules large enough to mainly remain within the vascular space and through colloid osmotic influence keep the administered fluid volume largely in the intravascular space. A colloid solution can therefore, at least in theory, provide a more rapid blood volume expansion with less volume given and consequently also less unwanted oedema formation. These basic physiological principles for the effects of colloids may, however, be compromised in situations such as sepsis and burn injury, where extensive capillary leakage may lead to increased extravasation of colloids. This makes the actual distribution of colloids difficult to predict, especially in the critically ill patients (Ernest, Belzberg *et al.* 1999⁴; van der Heijden, Verheij *et al.* 2009⁵).

There are three main types of synthetic colloid currently available: gelatins, dextrans and hydroxyethyl starch solutions. HES solutions which are derived of the partial hydrolysis of maize or potato starch, amylopectin, with replacement of the hydroxyl (OH) radicals (present in position C2, C3 and C6) by hydroxyethyl radicals are characterised by four elements: the molecular weight ranging from 70 to 670kDa, the degree of substitution which is usually 0.4 (tetrastarch) to 0.7 (hetastarch), the C2/C6 ratio characterizing the type of substitution (substitution is only possible at level 2, 3 or 6) and the concentration (generally 6% or 10%). Use of HES solutions has been associated with several problems. First, they alter hemostasis in a dose-dependent fashion. These alterations are primarily similar to a von Willebrand type of disease, as for dextrans. Second, HES solutions can persist in the organism sometimes for very prolonged periods of time, especially in the reticuloendothelial system. Third, these solutions may alter renal function, possibly as the result of the development of osmotic-nephrosis-like damage.

The PRAC considered all available data which includes recently published large clinical trials in critically ill patients and patients with sepsis, several meta-analyses as well as results of two unpublished clinical trials which compared HES with crystalloids and other colloids. The PRAC also consulted the views of experts through an Ad-Hoc Expert meeting.

2.1.1. Safety

Based on data from clinical studies, HES when compared to crystalloids was shown to be associated with an increased risk of mortality in patients with severe sepsis and adverse renal effects in particular in critically ill patients. A higher risk for other adverse reactions was also reported. These safety concerns which were reported in several clinical studies as well as meta-analyses are presented below.

Risk of mortality

Treatment with HES in critically ill patients has been associated with increased risk of mortality at day 90 in two large randomised clinical trials (including a recent published one) in patients with sepsis and septic shock (6S, VISEP).

The 6S study which was a randomised, multicentre, parallel-group, blinded trial was conducted in 804 patients (798 included in the modified intention-to-treat ITT population). The two intervention groups

⁴ Ernest D, Belzberg AS *et al.* Distribution of normal saline and 5% albumin infusions in septic patients. *Crit Care Med* 1999; 27(1): 46-50

⁵ van der Heijden M, Verheij J *et al.* Crystalloid or colloid fluid loading and pulmonary permeability, edema, and injury in septic and nonseptic critically ill patients with hypovolemia. *Crit Care Med* 2009; 37(4): 1275-81

had similar baseline characteristics. At day 90 after randomisation, 201 of 398 patients (51%) assigned to HES 130/0.42 had died, as compared with 172 of 400 patients (43%) assigned to Ringer's acetate (relative risk (RR), 1.17; 95% confidence interval [CI], 1.01 to 1.36; P = 0.03); 1 patient in each group had end-stage kidney failure.

In the randomised, multicentre, two-by-two factorial trial including 600 patients (VISEP Study), the rate of death at 28 days did not differ significantly between the HES group and the Ringer's lactate group (26.7% and 24.1%, respectively; P=0.48). However, mortality at day 90 was significantly increased in patients who received higher dose of HES 205/0.5 (>22 ml/kg bodyweight per day) compared to the Ringer's lactate group (41.0% vs 33.9%, P=0.09).

These findings were confirmed by recent meta-analyses (Zarychanski et al. 2013⁶; Cochrane review 2013⁷).

The meta-analysis (Zarychanski et al. 2013) included 38 trials with 10,880 critically ill patients and compared HES with crystalloids, albumins or gelatine. When 7 trials were excluded from an investigator whose subsequent research had been retracted because of scientific misconduct, HES was found to be associated with increased risk of mortality among 10290 patients (RR: 1.09; 95% CI): 1.02-1.17; (heterogeneity) I² 0%). A subgroup analysis of 12 randomised clinical studies that used 6% HES 130/0.4 formulations only, confirmed the increased risk of mortality in patients treated with HES.

In the Cochrane review, a 10 % higher mortality rate was shown for patients who received HES (RR: 1.10; 95% CI 1.02 - 1.19). It should be noted that two studies contributed to 80% of the weight in the meta-analyses (CHEST study Myburgh *et al.* 2012; 6S Study Perner *et al.* 2012) which were adequately powered and blinded, multicentre studies.

Adverse renal effects

The potential mechanism behind adverse renal effects associated with HES includes an increased uptake of starch into the renal epithelial cells inducing osmotic nephrosis, tubular obstructions by hyperviscous urine, and renal inflammation (Claus RA *et al.* 2010⁸). However, the potential mechanism is not fully elucidated. Adverse renal effects of HES, independent of the molecular weight or other differences in the product composition were reported in several clinical studies.

Safety data from clinical trials

- VISEP study (Brunkhorst FM *et al.* 2008)

The VISEP study was conducted as a multicentre, two-by-two factorial trial, in 600 patients (537 included for ITT analysis) with severe sepsis randomised to receive either intensive insulin therapy to maintain euglycemia or conventional insulin therapy and either 10% pentastarch, a high-molecular-weight 10% HES (HES200/0.5; hypertonic), or modified Ringer's lactate for fluid resuscitation. The rate of death at 28 days and the mean score for organ failure were co-primary end points.

The study results showed an increased rate of renal failure in patients with severe sepsis treated with HES (200/0.5) compared to patients treated with Ringer's lactate. At day 90, patients who had received HES, even when they received lower HES doses, were more likely to have renal failure than those who had received Ringer's lactate (30.9% vs. 21.7%, P = 0.04) and were more likely to need renal-replacement therapy (25.9% vs. 17.3%, P = 0.03). The PRAC acknowledged that a number of

⁶ Zarychanski, R., A. M. Abou-Setta, et al. (2013). Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. *JAMA* 2013; 309(7): 678-88

⁷ Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients (Cochrane review). *Cochrane Database Syst Rev* 2013; CD000567(2):1-73

⁸ Claus RA, Sossdorf M, Hartog C *et al.* The effects of hydroxyethyl starch on cultured renal epithelial cells. *Anesth Analg.* 2010 Feb 1; 110(2): 300-1

patients received higher dose of HES (200/0.5) (>22 ml/kg/d), however, the risk of RRT was also seen in patients treated with HES (200/0.5) at the recommended daily doses.

- 6S trial (Perner A *et al.* 2012)

The 6S trial is a randomised, multicentre, parallel-group, blinded trial which was conducted in 798 patients with severe sepsis receiving fluid resuscitation in ICU with either 6% HES (130/0.42) (n=398) or Ringer's acetate (n=400) at a dose of up to 33 ml per kilogram of ideal body weight per day. Septic shock was present in 84% of patients of both groups. The composite primary outcome was death or dependence on dialysis 90 days after randomisation.

In this 6S study, there was a significantly higher risk for RRT in patients in ICU treated with HES (130/0.42) (22% (87/398) compared to patients treated with Ringers' acetate (16% (65/400)) (RR: 1.35; 95% CI: 1.01-1.80; P=0.04). The results were supported by multivariate analyses, with adjustment for known risk factors for death or acute kidney injury at baseline.

The MAHs claimed that some patients in the trial appear to have received HES outside the indication hypovolemia. The MAHs claimed that since the median central venous pressure, S_vO_2 and lactate in each arm of the study were within the normal range, the patients were not hypovolemic when enrolled in the trial. The PRAC cannot endorse the MAHs interpretation and considered that central venous pressure, S_vO_2 and lactate can very well be in the normal range and still be compatible with clinical hypovolemia.

Furthermore, the PRAC acknowledged that a significant number of patients had acute kidney injury at randomisation, although renal failure with oliguria/anuria is a contraindication for HES. The patients with acute kidney injury at baseline were evenly randomised to the different treatment groups (142 in HES, 140 in Ringer's Acetate). Acute kidney injury occurred with equal frequency in the two intervention groups and the effect of HES 130/0.42 did not differ significantly between patients with and those without acute kidney injury at the time of randomisation. Therefore, the inclusion of the patients with acute kidney injury is unlikely to have affected the results of the study.

In conclusion, the suggested limitations of the 6S trial cannot be endorsed by the PRAC. The PRAC considered that the 6S study was well-designed and adequately powered. Due to the double blinding and the multi-center design of the study there is a low risk of bias.

The 6S study showed a significant higher risk for mortality at day 90 (see section on Risk of Mortality above) and need for RRT during the course of treatment in patients with severe sepsis and septic shock treated with HES (130/0.42) compared to Ringer's acetate.

- CHEST study (Myburgh *et al.* 2012)

The CHEST study is a randomised, multicentre, blinded, controlled study which was conducted in 7000 patients who had been admitted to an ICU in a 1:1 ratio to receive either 6% HES (130/0.4) in 0.9% sodium chloride or 0.9% sodium chloride (saline) for all fluid resuscitation until ICU discharge, death, or 90 days after randomisation. The main subgroups were: surgical (approximately 42%), sepsis (approximately 29%) and trauma (approximately 8%) patients.

Adult patients admitted to the ICU and whom the treating physician judged to require fluid resuscitation (bolus of intravenous fluid over and above that required for maintenance or replacement fluids) were included. It should be noted that some of the patients have been treated before randomisation. Fluid was administered to correct hypovolaemia at any time during the patients ICU admission. Patients who had received more than 1000ml of HES before screening were excluded.

In this study, RRT was administered to 7.0% (235/3352 patients) of patients treated with HES and in 5.8% (196/ 3375 patients) of patients treated with saline (RR: 1.21; 95% CI: 1.00-1.45; P = 0.04).

Indication for RRT was non-standardised and subjective. The decision when to start and stop RRT was purely dependent on the opinion of the physician (who were unaware of study group assignments) and may have included reasons other than reduced kidney function, such as over-hydration. This made it unlikely that the difference was caused by variations in the thresholds for initiating therapy.

This study also evaluated RIFLE criteria, which are composite of effects on serum creatinine levels and urine output. The results showed that renal risk (RIFLE-R) occurred significantly more often in the saline group (57.3%) as compared to the HES 130/0.4 group (54%; $p=0.007$). Likewise, renal injury (RIFLE-I) occurred more often in the saline group (38%) as compared to the HES 130/0.4 group (34.6%; $p=0.005$).

In view of these results, a post hoc analysis was conducted. The results showed that serum creatinine levels were significantly increased in the HES group suggesting a progressive reduction in creatinine clearance, and urine output was significantly decreased in the HES group, as compared with the saline group, during the first 7 days ($P = 0.004$ and 0.003 , respectively).

The PRAC noted that the number of patients who had chronic kidney disease at baseline has not been published, and the status of chronic kidney disease was also not specified. However, the following baseline data have been presented in the study publication. Serum creatinine in HES group was $101.5 \pm 57.1 \mu\text{mol/l}$ and $100.1 \pm 58 \mu\text{mol/l}$ in the saline group. Urine output 6 hours before randomisation was $453.5 \pm 418.3 \text{ ml}$ in the HES group and $426.6 \pm 422.9 \text{ ml}$ in the saline group. Therefore, there was no significant difference between both groups at baseline.

In conclusion, the CHEST study has shown an increased risk of RRT in patients treated with HES compared to the patients treated with 0.9% NaCl solution.

6S, CHEST and VISEP studies:

The PRAC has acknowledged the potential limitations of the studies presented by MAHs and noted the request from some MAHs for Good Clinical Practice (GCP) inspections to be conducted for the 6S, CHEST and VISEP studies. According to the MAHs the validity of these studies could be questioned due to potential flaws in their conduct. The PRAC has carefully considered the arguments presented by the MAHs. The PRAC also noted that the 6S study publication made clear reference to compliance with GCP. Notwithstanding the above, the PRAC considered that there was not sufficient evidence provided by the MAHs which would put into question the reliability of the study's results in relation to the identified risks.

- FIRST (Fluids in Resuscitation of Severe Trauma) trial (James MF *et al.* 2011)⁹

The FIRST trial was a randomized, controlled, double-blind study of severely injured patients requiring 3 litres of fluid resuscitation. Blunt and penetrating trauma were randomised separately. Patients were followed up for 30 days. A total of 115 patients were randomized; of which, 109 were studied.

When applying the RIFLE criteria, there was no difference between the groups in renal injury over 30 days between HES and saline groups. In the HES group significantly better lactate clearance and less renal injury than in the saline group was seen for patients with penetrating trauma. For the separately randomised group of patients with blunt trauma no advantage could be seen.

⁹ James MF, Michell WL, Joubert IA *et al.* Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: the FIRST trial (Fluids in Resuscitation of Severe Trauma). *Br J Anaesth* 2011;107(5): 693-702

- van der Linden *et al.* (2013)¹⁰

The review by van der Linden *et al.* assessed the safety of tetrastarches (HES 130, mostly HES 130/0.4) during surgery in 4529 patients. The control group (N=2390) was another colloid, a crystalloid, a blood product, a vasoactive drug or no other treatment.

No differences were seen for adverse renal effects or need for RRT, increased blood loss, allogeneic erythrocyte transfusion or mortality (odds ratio (OR) for HES mortality=0.51(0.24-1.05) P= 0.079; 11/956 deaths reported with tetrastarches and 22/928 in the comparator group).

However, it should be noted that most of the included studies had low numbers of patients between 20 and 90 patients (such as the study by Feldheiser *et al.* (2013)¹¹ (n=50) or Godet *et al.* (2008)¹² (n=65)), and the larger studies were conducted with between 184 and 203 patients.

Furthermore, the comparator groups were very heterogeneous, some of the studies compared tetrastarches (HES 130) to other HES products (pentastarches (substitution degree 0.5), hexastarch (substitution degree 0.6), hetastarch (substitution degree 0.7), albumin, gelatine, crystalloids, a blood product, a vasoactive drug or no other treatment. The volumes of 130/0.4 used in the studies were rather small compared to those in 6S and CHEST.

The surgery patient group included patients from major abdominal surgery as well as from orthopaedic surgery, patients with trauma or burns some of whom might not be severely ill with regard to their need of therapy of hypovolemia or hypovolemic shock. There is no information on the number of patients in need of intensive care. In addition, the review does not allow conclusions about sepsis patients.

In conclusion, due to different comparators, small sample sizes, rather small doses of HES 130, and very short follow-up periods, this study does not allow any conclusion on renal safety or mortality differences between the use of HES 130/0.4 and crystalloids. The review would only be able to detect extensive differences of HES to all comparators (which include also other HES products). In addition, data from the post-operative follow up period are lacking.

Safety data from meta-analyses

Recently conducted meta-analyses and systematic reviews confirm the increased rate of renal dysfunction in HES treated patients.

- Zarychanski R *et al.* (2013)

In the meta-analysis (Zarychanski *et al.* 2013) targeting critically ill patients, when 7 trials (involving 590 patients) by an investigator were excluded as previously mentioned, HES was found to be associated with increased risk for renal failure among 8725 patients (RR 1.27; 95% CI, 1.09 to 1.47; I² 26%) and an increased risk for RRT among 9258 patients (RR 1.32; 95% CI 1.15 to 1.50; I² 0%). The conclusion of the authors is that the use of hydroxyethyl starch for acute volume resuscitation is not warranted due to serious safety concerns.

¹⁰ Van der Linden P, James M, Mythen M, Weiskopf RB. Safety of modern starches used during surgery. *Anesth Analg* 2013; 116: 35-48

¹¹ Feldheiser A, Pavlova V, Bonomo T *et al.* Balanced crystalloid compared with balanced colloid solution using a goal-directed haemodynamic algorithm. *Br J Anaesth.* 2013; 110(2): 231-40.

¹² Godet G, Lehot JJ, Janvier G *et al.* Safety of HES 130/0.4 (Voluven(R)) in patients with preoperative renal dysfunction undergoing abdominal aortic surgery: a prospective, randomized, controlled, parallel-group multicentre trial. *European journal of anaesthesiology* 2008; 25: 986-994.

- Haase N *et al.*¹³

The meta-analysis by Haase *et al.* compared HES 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis. This systematic review with meta-analysis and trial sequential analysis includes some small studies (Dolecek M *et al.* and Palumbo D *et al.*) as well as the BaSES¹⁴, CHEST and 6S trials. Altogether nine trials have been included. The meta-analysis showed a higher risk of RRT for HES users (RR 1.36, CI 1.08 to 1.72, Trial sequential analysis (TSA) adjusted 1.03 to 1.80, 1311 patients, five trials), and a higher risk for acute kidney injury (RR 1.18, CI 0.99 to 1.40, TSA adjusted 0.90 to 1.54, 994 patients, four trials).

- Meta-analysis on HES in cardiovascular surgery

A meta-analysis initiated by one of the MAHs was performed to compare HES as volume expanders in cardiovascular surgery with other conventional volume expanders, namely, albumin, crystalloids and gelatin. The meta-analysis focuses on the harm outcomes total blood loss, frequency of blood transfusions, frequency of reoperations, frequency of acute kidney injury, and mortality.

No clear difference was seen comparing different types of HES to crystalloids. The overall methodological problems with this meta-analysis, however, substantially limit the conclusions that can be drawn. Some results support differences in favour of lower substitution ratio HES products but results are not consistent. No conclusions can be drawn from data on reoperation, acute kidney injury or mortality.

The main other adverse reactions reported in published clinical trials are presented below.

Coagulation system

Several studies have shown that HES was associated with platelet dysfunction, decrease of factor VIII and von Willebrand factor levels and interaction with the coagulation system. An increased bleeding tendency was not only detected with high molecular weight HES but also with low molecular weight HES.

In the 6S study more patients in the HES group received blood product transfusions with higher volumes than patients in the Ringer's lactate group (RR: 1.20; 95% CI: 1.07-1.36; p: 0.002). Patients in the HES group were at higher risk for severe bleeding events (P=0.09).

Results of the CHEST study also showed that the first 4 days, the HES group received significantly more blood products than the saline group (78±250 ml vs. 60±190 ml, P<0.001).

In the VISEP study, a significant lower platelet count in septic patients treated with 10% HES 200/0.5 (179,600 per cubic millimeter; interquartile range, 122,000 to 260,000) compared to Ringer's lactate group (224,000 per cubic millimeter; interquartile range, 149,800 to 314,800; P<0.001) was reported.

In the FIRST trial, the HES 130/0.4 group required significantly more blood products [packed red blood cell volumes 2943 (SD:1628) vs 1473 (SD:1071) ml, P=0.005] than the saline group and a significantly greater deterioration in coagulation measures was seen, although this could be due to greater injury severity.

¹³ Haase N, Perner A, Hennings LI, *et al.* Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. *Brit Med J* 2013; [Epub ahead of print]

¹⁴ BaSES Trial: <http://clinicaltrials.gov/show/NCT00273728>

In the CRYSTMAS trial¹⁵, 29% of patients in the HES group required red blood cell transfusion, compared to 21% in the control group (NaCl 0.9%).

Hepatic organ failure

The CHEST study reported a significantly higher incidence of new hepatic organ failure (in terms of S-Bilirubin increase) in the HES group than in the saline group (1.9% versus 1.2%; RR: 1.56; p=0.03). In addition, deposition of HES into hepatocytes has been reported in patients with worsening hepatic dysfunction (Christidis C *et al.* 2001¹⁶).

Anaphylactic reactions and pruritus

Anaphylactic reactions and pruritus are rather well characterised unfavourable effects of treatment with HES solutions for infusion. HES associated pruritus seems to be related to dosage.

In the CHEST study, the use of HES was associated with a significant increase in the rate of adverse events (5.3 vs. 2.8%, P<0.001). Of these events, pruritus and rash were the most common.

Conclusions on safety

The PRAC considered the data from recent published clinical trials as well as meta-analyses in the review of the safety of HES solutions for infusion in different patient populations. The three important studies that provided evidence for harm in septic patients or ICU patients including septic patients used three different HES products: 10% HES 200/0.45-0.55 in the VISEP study, HES 130/0.42 in the 6S trial and HES 130/0.4 in the CHEST trial. All three trials showed an increased risk for RRT or renal failure in patients treated with low and high molecular weight HES. The PRAC also considered that the use of HES solutions for infusion has been shown to be associated with an increased risk of mortality at day 90 (6S, VISEP studies). The PRAC acknowledged limitations of the above mentioned studies, but did not consider that they have an impact on the overall safety results. Furthermore, the PRAC considered that these data could be extrapolated to other populations such as trauma, burn injury, and elective surgery patients since they all experienced a systemic inflammatory response which is comparable in nature to the general population of critically ill or septic patients.

In view of the available data, the PRAC considered that the use of HES solutions for infusion has been shown to be associated with an increased risk of mortality and renal replacement therapy or renal failure. In addition, the PRAC took note of the available data showing an increased risk of adverse reactions in patients treated with HES such as increasing bleeding, hepatic organ failure, anaphylactic reactions and pruritus.

2.1.2. Efficacy

HES solutions for infusion are used in the setting of hypovolaemia to expand plasma volume. Colloidal solutions are used to sustain intravascular oncotic pressure and to shorten circulatory stabilisation time. Less amount of fluid for resuscitation is needed when compared to crystalloids.

The PRAC considered the dataset submitted by the MAHs. A critical assessment of studies as well as meta-analyses where HES was used has been performed.

¹⁵ Guidet B, Martinet O, Boulain T *et al.* Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: The CRYSTMAS study. *Crit Care.* 2012 May 24;16(3):R94

¹⁶ Christidis C, Mal F, Ramos J *et al.* Worsening of hepatic dysfunction as a consequence of repeated hydroxyethylstarch infusions. *J Hepatol* 2001; 35:726-32

Critically ill patients / ICU patients

The assessment of the CHEST study in critically ill patients, as well as the results of two recent meta-analyses (Perel P *et al.* 2012; Zarychanski R *et al.* 2013), are discussed in the following section. In addition, the PRAC took note of the results of an unpublished clinical trial (CRYSTAL study¹⁷).

- The CHEST study (Myburgh JA *et al.* 2012)

The results showed that a total of 597 of 3315 patients (18.0%) in the HES group and 566 of 3336 (17.0%) in the saline group died (RR in the HES group: 1.06; 95% CI: 0.96-1.18). There was no significant difference between HES group and the saline group.

The use of HES was associated with the administration of lower volumes of resuscitation fluid, although the ratio between HES and saline was similar to that observed in other blinded trials, suggesting that the use of HES was not associated with a substantive volume-sparing effect (6S study, CRYSTMAS trial, James *et al.*). There was no clinically meaningful volume-sparing effect of HES.

Therefore, the CHEST study does not provide evidence that resuscitation with 6% HES (130/4), as compared with saline, in the ICU provided any clinical benefit to the patient. Moreover as previously discussed, the results showed that treatment with HES in critically ill patients has been associated with an increased risk of RRT.

A limitation of the study is that the observed rate of death was lower than predicted. In addition, patients were recruited after admission to the ICU, when the requirements for fluid resuscitation are often less than those for patients in the emergency department or the operating room. Despite these limitations, the trial had sufficient statistical power to detect an absolute mortality difference of 3 percentage points.

These findings have been strengthened by two recent meta-analyses (Cochrane Review: Perel P *et al.* 2013; Zarychanski R *et al.* 2013) (see section Risk of mortality).

In conclusion, there was no clinically meaningful volume-sparing effect of HES in this patient population. Therefore, no benefit with HES has been demonstrated in this population of patients.

- CRYSTAL study

The Efficacy and Safety of Colloids Versus Crystalloids for Fluid Resuscitation in Critically Ill Patients (CRYSTAL) by Annane *et al.* trial compared any type of colloid versus any type of crystalloid in ICU patients who needed fluid resuscitation with the primary endpoint day 28 mortality. Secondary outcome measures were ICU and hospital mortality rates, number of days free of mechanical ventilation, vasopressors, renal replacement therapy, and organ system failure (90 days), difference in the area under the curve of MAP from inclusion to hour 24, weight gain, PaO₂/FiO₂ ratio, chest x ray score (day 2), frequency of adverse events (90 days) and length of stay. The time between the decision to resuscitate a patient with fluids and randomisation was kept as short as possible (15 minutes or less). The amount of HES was not allowed to exceed 30 ml/kg/24 hours. According to the protocol, the starch cumulative dose was planned to be limited to 35/40 ml/kg for all ICU stay. In case additional volume replacement was necessary, gelatines or albumin could be used. Groups were stratified by site and diagnosis: 1. Trauma or haemorrhage, 2. Sepsis, 3. other diagnoses. Blinding was considered unfeasible, except primary endpoint was assessed by a blinded assessor. In the colloid group, 774 (54.7%) of patients were included in the sepsis stratum and compared to 779 (54.0 %) in the crystalloid group. More than 40 % of the colloid group received HES (30% received gelatine).

¹⁷ Annane, D. The CRYSTAL trial. 2013. CRISTAL Trial: <http://clinicaltrials.gov/ct2/show/NCT00318942>
SLRF 2013, CRYSTAL, Annane D <http://www.srlf.org/congres/ancien-congres/2013/index.phtml>.

First data were presented in January 2013 in Paris (41 Congrès International de la Société de Réanimation de Langue Française). On day 28, the mortality in the colloid arm was 25.4 % versus 27 % in the crystalloid arm ($p=0.30$, primary endpoint). On day 90, 30.7 % of patients died in the colloid arm versus 34.2 % in the crystalloid arm ($p=0.04$). The odds ratio was 0.90 (95 % CI: 0.745-1.082) which is a non-significant trend in favour of colloids as regards the primary endpoint 28- day mortality. For the 90 day mortality the odds ratio was 0.83 (95 % CI: 0.693-0.948).

Although, the MAHs claimed that the preliminary results of the study show a clinical benefit of HES in critically ill patients, the data of this study have not been published at the time of this discussion nor was a full report available and therefore further assessment is required before any conclusion can be drawn.

Sepsis

A number of results from several large, overall well-conducted randomised clinical trials have been identified as a basis for a benefit-risk assessment of HES in patients with sepsis. The critical assessment of three recent published clinical trials (6S, CRYSTMAS, VISEP) and an observational cohort study (Bayer O *et al.* 2012¹⁸) is presented below. In addition, the PRAC considered the review of the results of unpublished clinical trial (BaSES study¹⁹) which were presented by one of the investigators of this study during an oral explanation in June 2013 PRAC meeting.

- 6S trial (Perner A *et al.* 2012)

The results of the study showed a significantly higher mortality at day 90. There were 51% (201/398) of the patients in the HES 130/0.42 group versus 43% (172/400) in the Ringer's acetate group who died (RR: 1.17; 95% CI 1.01-1.36; $P= 0.03$). The results were supported by multivariate analyses, with adjustment for known risk factors for death or acute kidney injury at baseline. Doses were given up to 33 mL/ideal bodyweight/day. As in the CHEST study, there does not appear to be any volume sparing effect of HES, which would be expected to be the main benefit from a colloid.

Therefore, the study 6S did not show any benefit of HES for patients with severe sepsis.

Limitations of this study are addressed below.

The MAHs claimed that many patients in the 6S study were already haemodynamically stable at baseline, and therefore a volume replacement solution was not indicated in these patients. The PRAC considered that baseline characteristics were comparable in both groups and that there was no significant difference in blood products given before randomisation between the groups (packed red blood cells, fresh frozen plasma, platelets). One of the MAH stated that patients in the HES group might have been more ill than those in the Ringer's acetate group. Patients in the HES group had more emergency admissions, but only 27% versus 24%, so that it seems unlikely that the unfavourable results could be explained by this small difference. Therefore, the PRAC considered that there is no evidence in the baseline characteristics indicating that HES treated patients were more severely ill than patients in the Ringer's acetate group.

Even though most of the patients in the 6S trial had fluid volume therapy 24 hours before randomisation the criteria for hypovolemia for the patients were fulfilled. 336/398 (84%) of the patients in the HES group and 337/400 (84%) in the Ringer's acetate group had shock at randomisation which was defined as a mean arterial pressure of less than 70 mm Hg, the need for on-

¹⁸ Bayer O, Reinhart K *et al.* Effects of fluid resuscitation with synthetic colloids or crystalloids alone on shock reversal, fluid balance, and patient outcomes in patients with severe sepsis: A prospective sequential analysis. *Critical Care Medicine* 2012; 40(9): September

¹⁹ BaSES Trial: <http://clinicaltrials.gov/show/NCT00273728>

going treatment with vasopressor or inotropic agents, or a plasma lactate level of more than 4.0 mmol/L in the hour before randomisation. Patients with severe sepsis were randomly assigned to receive fluid resuscitation in the ICU. The trial definition of fluid resuscitation was a bolus of intravenous fluid which was given to increase intravascular volume, the fluid should be given in addition to that required to replace on-going insensible losses, urinary losses etc. or for nutrition. However, inclusion criteria were the same for each fluid group and thus both groups are comparable.

No substantial differences were found with regard to the study fluid amounts of HES compared to Ringer's acetate in patients with severe sepsis.

The 6S study was well-designed and adequately powered. Due to the double blinding and the multi-center design of the study there is a low risk of bias. The vehicle of HES used in the intervention group was Ringer's acetate. Since Ringer's acetate was also used as control, the causal effect of HES on outcomes can be assessed.

- VISEP study

In the randomised, multicentre, two-by-two factorial trial including 600 patients (VISEP Study), the rate of death at 28 days did not differ significantly between the HES group and the Ringer's lactate group (26.7% and 24.1%, respectively; $P=0.48$). However, mortality at day 90 was significantly increased in patients who received higher dose of HES 205/0.5 (>22 ml/kg bodyweight per day) compared to the Ringer's lactate group (41.0% vs 33.9%, $P=0.09$).

- CRYSTMAS trial (Guidet B *et al.* 2012)

The CRYSTMAS trial is a prospective, multicentre, controlled, double blinded randomised trial which was conducted in 196 patients with severe sepsis, where 100 patients received HES and 96 patients received sodium chloride 0.9%. The primary endpoint of the study was the amount of study drug required to achieve initial hemodynamic stabilisation (HDS).

The results of the study showed that an about 20% less amount of HES 130/0.4 was needed to achieve circulatory stabilisation of septic patients in the initial phase of resuscitation compared to saline. However, the reduction in volume requirement was not clinically relevant (while statistically significant) and the total amount of study fluid over 4 days was similar for HES and saline. Therefore, the PRAC was of the opinion that the volume sparing effect observed in this study did not translate in clinical benefit for patients.

The study was not powered to show differences in mortality or kidney function.

- Cohort study (Bayer O *et al.* 2012)

The study was a non-randomised observational cohort study which compared HES (predominantly 6% HES 130/0.4), 4% gelatine, and crystalloids in 1046 patients with severe sepsis (HES $n=360$; gelatine $n=352$ and crystalloids $n=334$). The primary outcome was time to shock reversal and the secondary endpoint was required fluid volumes in severe sepsis.

The results showed that all groups had similar time to shock reversal ($P=0.68$). More fluid was needed over the first 4 days in the crystalloid group (fluid ratios 1.4:1 [crystalloids to HES] and 1.1:1 [crystalloids to gelatine]). After day 5, fluid balance was more negative in the crystalloid group. HES and gelatine were independent risk factors for acute kidney injury (OR: 95% CI: 2.55, 1.76-3.69 and 1.85, 1.31-2.62, respectively).

Therefore, according to the data shock reversal was achieved equally fast with synthetic colloids or crystalloids. Use of colloids resulted in only marginally lower required volumes of resuscitation fluid.

As this is a non-randomised observational cohort study with a sequential design, the possibility of systematic differences between the two groups reflecting non-measured alterations in other aspects of therapy, or period effects as a result of general improvements in the care of septic patients cannot be ruled out. Furthermore, it cannot be excluded that uncontrolled changes in treatment patterns such as changes in end of life decisions may have contributed to the decreased length of stay on the ICU and reduced time on the ventilator over the three sequential study periods.

- BaSES study

The PRAC further considered the results of an unpublished clinical study, the BaSES study. The results of this study were presented by one of the investigator during an oral explanation at PRAC in June 2013.

The BaSES (Basel Starch Evaluation in Sepsis) trial was a single centre investigator-initiated study performed in Basel, Switzerland and first presented at the European Society of Anaesthesiology (ESA) conference in June 2012. This double-blind, randomised study included 241 patients with severe sepsis and septic shock treated with 6% HES (117/241) or crystalloid (124/241). Both groups received additional infusion of Ringer's lactate solution. Mortality among ICU patients (6% HES: 28% vs. crystalloid: 29%) and hospital mortality (6% HES: 30% vs. crystalloid: 31%), as well as renal function parameters, did not differ between groups. However, there was a significantly reduced hospital length of stay in favour of 6% HES (6% HES : 20 days, vs. crystalloid: 28.5 days).

However, the data of the study have not yet been published and therefore further assessments are necessary before any conclusion can be drawn.

The two studies (6S, VISEP) have shown a significant higher mortality at day 90 in patients with severe sepsis and septic shock. The observational cohort study (Bayer *et al.*) did not show any difference between HES and crystalloids with regard the time to shock reversal. The PRAC took note of the results of the BaSES study suggesting a benefit of HES over crystalloids in critically ill patients and patients with sepsis. However, the PRAC considered that the available data coming from this study are limited as the study is not published nor a full report is available, and therefore require further assessment before any conclusion can be drawn.

In addition to the above PRAC noted that recent clinical guidelines do not recommend use of HES in this patient population. The Surviving Sepsis campaign guideline²⁰ which was updated in 2012 does not recommend the use of HES for fluid resuscitation in patients with severe sepsis or septic shock because of the absence of any clear benefit following the administration of colloid solutions compared to crystalloid solutions. A high grade recommendation for the use of crystalloid solutions in the initial resuscitation of patients with severe sepsis and septic shock is supported.

Since 2008, the German S-2k guideline²¹ (Deutsche Sepsis-Gesellschaft) also recommends against the use of HES 200/0.5 and HES products with lower molecular weight because of lack of data.

The present available data do not show any benefit for HES when compared to crystalloids for the patients with severe sepsis and septic shock. Overall PRAC considered that for subjects with severe sepsis or septic shock the risks of increased mortality (and more frequent use of RRT) are considered to outweigh the limited benefits of more rapid attainment of hemodynamic stability compared to crystalloids.

²⁰ Dellinger RP, Levy MM, Rhodes A *et al.* Surviving Sepsis Campaign: International guidelines for Management of severe Sepsis and Septic Shock. *Intensive Care Med.* 2013; 39(2):165-228

²¹ Reinhart K, Brunkhorst FM, Bone HG *et al.* Prevention, diagnosis, therapy and follow-up care of sepsis: 1st revision of S-2k guidelines of the German Sepsis Society (Deutsche Sepsis-Gesellschaft e.V. (DSG)) and the German Interdisciplinary Association of Intensive Care and Emergency Medicine (Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin (DIVI)). *Ger Med Sci.* 2010; 8: Doc14.

Burn injury

Few data are available supporting the use of HES in burns.

The pilot open-label randomised study from Sudhakar *et al.* (2008)²² investigated the safe use of HES for initial resuscitation and if early treatment can reduce crystalloid overload in burned patients. HES doses were given up to 20 mL/kg in 48 hours, post burn parameters for oedema were more favourable for HES, significantly more patients in the crystalloid group died (9/10 (90%) versus 11 /22(50%)). Patients in the crystalloid group had 7% more total burn surface at admission.

Although the results suggested a more rapid response to HES compared to crystalloids, severe methodological issues have been identified meaning that no efficacy or safety (both short time and long-time) conclusion can be drawn from this study.

With the negative effect seen on mortality in sepsis, the well demonstrated deposit of HES in tissues, and the pathophysiological similarities between sepsis and early burn injury physiology with a massive inflammatory response and capillary leakage, the benefit-risk of HES in burns cannot presently be considered favourable.

Trauma patients

Trauma patients constitute an important subgroup of patients with particular considerations needed. Trauma was included as a pre specified subgroup analysis in a recent meta-analysis (Zarychanski *et al.* 2013) which included five studies (Nagy K *et al.* 1993²³; Younes RN *et al.* 1998²⁴; Carli P *et al.* 2000²⁵; James MF *et al.* 2011; Myburgh JA *et al.* 2012; Myburgh JA *et al.* 2013²⁶). There was no signal of benefit, if anything there appeared to be an increase in mortality associated with HES (RR 1.24 (0.81, 1.90)).

Figure 1: Outcome in trauma patients (Zarychanski *et al.* 2013)

Outcome or Subgroup	Studies	Participants HES (n/N) Control(n/N)		Effect estimate (CI)	I ² (uCI)
Trauma ^{4,23,48,51,54}	5	45/ 434	35/ 430	RR 1.24 (0.81, 1.90)	0% (0%, 75%)

The FIRST trial (James MF *et al.*) in trauma patients provides information on the comparison to the use of HES 130/0.4 versus salines (NaCl 0.9%), but not on the effect on mortality or renal dysfunction. In this randomised, controlled, double-blind study of severely injured patients requiring 3 litres of fluid resuscitation, patients were followed up for 30 days. Blunt and penetrating trauma were randomised separately. A total of 115 patients were randomised; of which, 109 were studied. For patients with penetrating trauma (n=67), the mean (SD) fluid requirements were 5.1 (2.7) litres in the HES group and 7.4 (4.3) litres in the saline group (P, 0.001). In blunt trauma (n=42), there was no difference in study fluid requirements, but the HES group required significantly more blood products as previously mentioned. Although the study showed a positive effect of HES in penetrating trauma patients, the results need further confirmation due to the relatively low number of events.

²² Sudhakar GV *et al.* Role of HES 130/0.4 in resuscitation of patients with major burn injury. *Transfus Altern Transfus Med* 2008; 10(2): 43/50

²³ Nagy K. *et al.* A comparison of pentastarch and lactated Ringer's solution in the resuscitation of patients with hemorrhagic shock. *Circ Shock* 1993; 40(4): 289-94.

²⁴ Younes RN *et al.* Use of pentastarch solution in the treatment of patients with hemorrhagic hypovolemia: randomized phase II study in the emergency room. *World J Surg* 1998; 22(1): 2-5

²⁵ Carli P *et al.* (2000). Remplissage vasculaire prehospitalier en traumatologie: hesteril 6% versus plasmion. *Jeur* 2000; 13(1-2): 101-105.

²⁶ Myburgh JA *et al.* Hydroxyethyl starch or saline in intensive care. *N Engl J Med* 2013; 368(8): 775

In this study, the volume of clear fluids (crystalloids) administered was half of that given in other trials where an association with compartment syndrome and gastrointestinal dysfunction with high volumes of crystalloids could be seen. In addition, severe abdominal compartment syndrome was only seen in patients receiving very large crystalloid loads. The absence of any difference in recovery of gut function and the low incidence of abdominal compartment syndrome suggest that in trauma patients, reasonable fluid resuscitation is not a major risk factor. However, this study only gives sparse information on whether patients with penetrating trauma and a need for high fluid volume have a benefit when treated with HES.

In view of the limited benefit of HES in this setting, and the potential harm as referred above the benefit risk ratio is not considered favourable.

Elective surgery

Several studies in surgery patients with HES have been presented by the MAHs. The vast majority of the studies presented could only provide limited information since only comparisons with other HES solutions were made. The critical assessment of clinical trials published by Standl T *et al.* 2008²⁷ and Mercier FJ *et al.* 2011²⁸ as well as the study published by Madi-Jebara *et al.* 2004²⁹ and Feldheiser *et al.*³⁰ are presented below.

- Standl T *et al.* 2008

A prospective, randomised, open-label pilot study conducted in paediatric patients less than 2 years of age compared HES 130/0.4 to albumin 5% in cardiac and non-cardiac surgery. The results of the study showed similar efficacy profiles between both treatments (observation time until hospital discharge). Therefore, in this study, short term efficacy for HES 130/0.4 seems equal with albumin when used as volume expander in small children. However, the limited observation time and number of studied children prevents any conclusions of the overall efficacy profile of HES 130/0.4 in this population.

- Mercier FJ *et al.* 2011

The phase IV, randomised, controlled, blinded clinical trial compared 500 mL HES 130/0.4, 6% + 500 mL Ringer's lactate vs 1000 mL Ringer's lactate in the context of spinal anaesthesia for caesarean section in 167 patients. The results of the study showed hypotension periods in 37% in the HES group and in 55% in the Ringer's lactate group. HES could be detected in umbilical cord. The results suggested that short term efficacy seems better for HES compared with Ringer's lactate when equal amounts of volume are administered. It should be noted that this comparison is of limited relevance. A larger volume of Ringer's lactate is needed to generate a comparable plasma volume expansion as HES. Any crystalloid/colloid comparison needs to take this fact into account. Consequently, the addition of Ringer's lactate in the HES group, made in order to facilitate blinding, distorts the comparison. Lower incidence of hypotension is therefore expected and the results are of limited clinical relevance. A volume sparing effect has not been demonstrated and relevance of the short-term hemodynamic differences is unclear since potential long-term effects are not studied.

²⁷ Standl T, Lochbuehler H, Galli C *et al.* HES 130/0.4 (Voluven®) or human albumin in children younger than 2 yr undergoing non-cardiac surgery. A prospective, randomized, open label, multicentre trial. *Eur J Anaesthesiol* 2008; 25(6): 437-45

²⁸ Mercier FJ, Diemunsch P, Ducloy-Bouthors A *et al.* 6% HES (130/0.4) vs. Ringer's Lactate to Prevent Hypotension during Spinal Anesthesia for C-section. American Society of Anesthesiologists (ASA), Annual Meeting 2011; A973

²⁹ Madi-Jebara S, Goshn A, Cherfane A, *et al.* Prevention of hypotension after spinal anesthesia for caesarean section: Voluven (6% hydroxyethyl starch 130/0.4) versus lactated Ringer's solution. *Anesthesiology* 2004; 101(suppl): A1197

³⁰ Feldheiser A, Pavlova V, Bonomo T, Jones A, Fotopoulou C, Sehouli J, Wernecke KD, Spies C. Balanced crystalloid compared with balanced colloid solution using a goal-directed haemodynamic algorithm. *British journal of anaesthesia* 2013 ; 110(2):231-40

- Madi-Jebara *et al.* 2004

The study was a randomised, open label study comparing HES 130/0.4, 6% (500 mL) with Ringer's lactate (1000 mL) in 120 patients with elective caesarean section. The results of the study showed that hypotension occurred in 64% in the HES group and 81% in the Ringer's lactate group. The study suggested that HES 130/0.4 6% seems to have benefits over twice the volume of Ringer's lactate in preventing spinal anaesthesia induced hypotension. The advantages for preloading with HES 130/0.4 6% are small but measurable when only spinal anaesthesia is used.

- Feldheiser *et al.* 2013

The Feldheiser study targets major elective surgery studying 50 patients undergoing major cancer surgery. It is however a small study (by the authors characterised as a pilot study where tests should be considered exploratory) and not powered to study long-term mortality. In the short term, the study indicated a benefit for the HES group in maintaining a better cardiac output with less volume given (Time to reach 50 mL/kg: HES = 2:26 h, crystalloids = 3:33 h).

Overall, it appears to be a difference in hemodynamic variables when HES is used for preload during spinal anaesthesia, as compared to Ringer's solution. Benefit for elective surgical patients has been shown in short-term surrogate hemodynamic outcomes along with a modest volume sparing effect (mean crystalloid-colloid ratio 1.8, SD 0.1) (Hartog *et al.* 2011³¹). Studies in elective surgery have not been performed in sufficiently large populations and had a sufficiently long follow-up time to allow any conclusions about risks for mortality and use of RRT. In view of the limited benefit and the potential harm as referred above the benefit risk ratio is not considered favourable.

In addition, the PRAC took note of a meta-analysis initiated by one of the MAHs which compared HES as volume expanders in cardiovascular surgery with other conventional volume expanders, namely, albumin, crystalloids and gelatin. The meta-analysis focuses on the harm outcomes total blood loss, frequency of blood transfusions, frequency of reoperations, frequency of acute kidney injury, and mortality. The PRAC noted that no assessment of bias in the underlying studies is made. In addition, the PRAC highlighted that the design issues are not in line with the PRISM guidelines for meta-analyses. The PRAC was of the opinion that the report does not provide a conclusion for HES degree of substitution 0.45 (tetrastarch) compared to albumin but the result appears to favour albumin as does the results for HES degree of substitution 0.7 (hetastarch). The results for HES 0.4 appear to favour HES but results are sensitive to the definition of blood loss. The overall methodological problems with this meta-analysis substantially limit the conclusions that can be drawn. No clear difference was seen comparing different types of HES to crystalloids.

Conclusion on efficacy

In view of the available data, the PRAC is of the opinion that HES solutions for infusion do not provide any clinical benefit in critically ill patients over crystalloids. There was no clinically meaningful volume-sparing effect of HES in this patient population. For subjects with severe sepsis or septic shock the risks of increased mortality (and more frequent use of RRT) are considered to outweigh the limited benefits of more rapid attainment of hemodynamic stability compared to crystalloids. The PRAC also considered that studies on trauma and elective surgery only showed limited clinical benefit of HES. Furthermore, evidence is not found that resuscitation with colloids reduces the risk of death in patients with trauma, burns, or after surgery when compared to crystalloids.

³¹ Hartog C, Kohl M, *et al.* "A systematic review of third-generation hydroxyethyl starch (HES 130/0.4) in resuscitation: safety not adequately addressed. *Anesth Analg* 2011; 112(3): 635-45

Ad-hoc Expert group

The PRAC also consulted the views of experts through an Ad-Hoc Expert meeting.

The expert group agreed that the now consistent hydroxyethyl starch (HES) data for harm in patients with sepsis could be extrapolated to patients with burn injury, mixed conditions needing critical care units' resources, trauma, elective surgery patients and in any other clinical setting.

The expert group considered that these data could be extrapolated to these patient groups, since they all experience a systemic inflammatory response which is comparable in nature to the general population of critically ill or septic patients. Moreover, as these patients are at risk of developing critical illness, they are therefore also at risk of developing harm from the prior administration of starch-based intravenous fluids.

The expert group considered that there is no patient relevant benefit (like hospital length of stay or survival) for the patients in taking HES above and beyond surrogate parameters and they could not identify any subgroup of patient who should or should not be included. This view is supported by several peer-reviewed research studies. The group were therefore of the view that patients in these clinical groups were at increased risk of harm from starch-based intravenous fluids.

3. Overall discussion and risk/benefit assessment

The PRAC considered all available data which includes recently published large clinical trials in critically ill patients and patients with sepsis, several meta-analyses as well as results of two unpublished clinical trials which compared HES with crystalloids and other colloids. The PRAC also consulted the views of experts through an Ad-Hoc Expert meeting.

The PRAC is of the opinion that HES do not provide any clinical benefit in critically ill patients over crystalloids. There was no clinically meaningful volume-sparing effect of HES in this patient population. For subjects with severe sepsis or septic shock the risks of increased mortality (and more frequent use of RRT) are considered to outweigh the limited benefits of more rapid attainment of hemodynamic stability compared to crystalloids. Furthermore, evidence is not found that resuscitation with colloids reduces the risk of death in patients with trauma, burns, or after surgery when compared to crystalloids.

PRAC also considered that the use of HES for solutions for infusion has been shown to be associated with an increased risk of mortality and renal replacement therapy or renal failure. HES is also associated with other serious adverse reactions such as increased bleeding, hepatic organ failure, anaphylactic reactions and pruritus.

In view of the available data, the PRAC concluded that the benefit risk balance of hydroxyethyl starch solutions for infusion is not favourable in the approved indications and in any patient population.

4. Re-examination procedure

Following the adoption of the PRAC recommendation during the June 2013 PRAC meeting, re-examination requests were received from several MAHs involved in the procedure, including Fresenius Kabi Deutschland GmbH, B. Braun Melsungen AG and Serumwerk Bernburg AG on 16th of August 2013. The scope of the re-examination focused on the re-evaluation of the benefit-risk of HES solutions for infusion in the treatment of hypovolaemia and hypovolemic shock in patient populations under specific settings (e.g. surgery and trauma).

It is noted that the PRAC is a scientific committee and that while it operates within the legal framework, it cannot discuss the specific merits of procedural and legal aspects of administrative

procedures laid down in the legislation. As a result, procedural and legal considerations are outside the remit of the PRAC, and therefore the re-examination of the referral procedure under Article 31 of Directive 2001/83/EC focused only on the scientific grounds for re-examination.

Detailed grounds for re-examination submitted by the MAHs

The MAHs disagreed with the negative benefit risk assessment of the PRAC of HES solutions for infusion:

- The MAHs considered that the beneficial effects for HES with regard to volume-stabilising effect and volume resuscitation as well as hemodynamic endpoints have been shown in several patient populations (e.g. surgery, trauma) and these have not been adequately assessed by the PRAC.
- The MAHs considered the extrapolation of study results derived from septic and critically ill patients to all other patients groups and indications not justified.
- The MAHs considered that the main studies (VISEP, 6S, CHEST) which were the main basis of the PRAC recommendation have strong limitations concerning study design and conduct. The MAHs considered that in these studies, many patients received HES solutions, although they were already haemodynamically stabilised at baseline meaning that many of those patients had no need for volume therapy and/or were partly overdosed.
- The MAHs considered that two clinical trials (BASES and CRYSTAL) have not been adequately assessed by the PRAC and that the results of these trials could potentially have a major impact on the conclusions of the procedure.
- The MAHs considered that spontaneous report on HES are rare compared to the number of patients under treatment with HES containing medicinal products
- The MAHs also considered that alternative synthetic colloids (e.g. dextran, gelatin) are less studied than HES and do not represent better alternatives (e.g. risk of anaphylactoid reactions). The MAHs further highlighted that safety data evaluated since registration of the HES products have not shown higher risk of mortality or higher risk of negative effects on renal functions.

The MAHs therefore considered that the benefit risk balance of HES solutions for infusion in the treatment of hypovolaemia and hypovolemic shock is positive in some patient populations (e.g. surgery, trauma).

PRAC conclusion on grounds for re-examination

The PRAC confirmed that it considered the totality of the data available in the context of the initial recommendation of the article 31 referral procedure. The PRAC reiterated that three important studies have shown evidence of harm in septic patients or ICU patients when HES products were administered (VISEP, 6S and CHEST). The studies' results reflect the clinical practice in the participating centres with regards to fluid resuscitation. In clinical practice patient history and clinical situation together with trends in various clinical variables are weighted together and treatment for hypovolemia is attempted. The results also showed an increase risk for RRT or renal failure in those treated HES; limitations have been previously discussed and were acknowledged.

Data available from studies in other patient populations, looking into volume-sparing effect and haemodynamic endpoints (e.g. Hanart C *et al.* 2009³², Feldheiser A *et al.* 2013³³, James MF *et al.*

³² Hanart C, Khalife M, De Villé A, et al. Perioperative volume replacement in children undergoing cardiac surgery: Albumin versus hydroxyethyl starch 130/0.4. *Crit Care Med* 2009; 37(2):696-701

2011, Neff *et al.* 2003³⁴; Myburgh *et al.* 2012; Ogilvie *et al.* 2010³⁵) have also been considered. However, the studies' results were of limited value, as sample sizes were either too small, imbalances were noted, or there was short follow up and inappropriate control. Other meta-analysis (e.g. Van der Linden *et al.* 2013) do not allow thorough conclusions as studies with small sample sizes, low doses of HES, short follow up and different comparators including an experimental hemoglobin solution and comparison with other HES solutions were included. Gattas DJ *et al.* 2013³⁶; Wiedermann CJ *et al.* 2012³⁷ have also shown safety concerns, namely an increased risk for death (Gattas DJ *et al.* and Wiedermann CJ *et al.*) and renal replacement therapy (Gattas DJ *et al.*). The MAH's meta-analysis on HES in cardiovascular surgery had also been considered before. No clear difference was seen between HES and crystalloids, and although some results did support differences in favour of lower substitution ratio HES products, some limitations were noted. The MAHs further referred to a number of small studies or meta-analysis in support of the use of HES 130/0.4 in surgical patients (e.g. Kasper *et al.* 2003; Gallandat-Huet *et al.* 2000; Ickx *et al.* 2003; Magder *et al.* 2010; Martin *et al.* 2013). The evidence for improved volume sparing effect observed in these studies, which is considered a surrogate endpoint, must be balanced against the lack of evidence to demonstrate benefits in relation to longer-term, clinically meaningful endpoints.

With regards to alternatives, the PRAC considered that there is no evidence from well-designed head to head comparisons that other colloids are associated with more or less serious risks compared to HES solutions.

The MAHs argued that the spontaneous adverse drug reactions (ADR) reports on HES have to be taken into consideration for the safety evaluation of HES. The PRAC noted that due to limited number of cases reported this data is of limited added value. It is well known that frequencies of certain ADRs as well as causality cannot be determined through passive adverse reaction reporting.

With regards to the evidence from CRYSTAL and BaSES studies, only preliminary results were available for the initial assessment in the referral under Article 31 of Directive 2001/83/EC. The PRAC acknowledged that new results became available after finalisation of the initial assessment of the referral under Article 31 of Directive 2001/83/EC and the MAHs claimed new evidence of a clinical benefit. The PRAC recognised that new evidence could be of relevance but these new data do not fall within the scope of this referral under Article 31 and therefore cannot be considered. These new data were nevertheless assessed in the referral on HES on the basis of Article 107i of Directive 2001/83/EC that was conducted separately but in parallel to the re-examination of the referral under Article 31 of Directive 2001/83/EC.

In addition, the PRAC consulted another *ad hoc* expert group that was convened on 13 September 2013. The *ad hoc* expert group was requested to clarify whether from a clinical perspective, given the available data and taking into account the increased risk of renal events and the increased mortality, there are subpopulations of critically ill patients (defined as patients admitted to the ICU) for whom HES treatment remains beneficial. Some experts considered that subpopulations of critically ill patients can be identified for whom treatment with HES remains beneficial such as all critically ill patients in emergency, all patients from ICU including limited trauma patients before surgery. However, the

³³ Feldheiser A, Pavlova V, Bonomo T, et al. Balanced crystalloid compared with balanced colloid solution using goal-directed haemodynamic algorithm. *Br J Anaesth* 2013; 110(2): 231-40

³⁴ Neff TA, Doelberg M, Jungheinrich C, et al. Repetitive large-dose infusion of the novel hydroxyethyl starch 130/0.4 in patients with severe head injury. *AnesthAnalg* 2003; 96(5): 1453-9

³⁵ Ogilvie MP, Pereira BM, McKenney MG, McMahon PJ, Manning RJ, Namias N, Livingstone AS, Schulman CI, Proctor KG. First report on safety and efficacy of hetastarch solution for initial fluid resuscitation at a level 1 trauma center. *Journal of the American College of Surgeons* 2010; 210: 870-80, 880

³⁶ Gattas DJ, Dan A, Myburgh J, Billot L, Lo S, Finfer S; CHEST Management Committee. Fluid resuscitation with 6% hydroxyethyl starch (130/0.4 and 130/0.42) in acutely ill patients: systematic review of effects on mortality and treatment with renal replacement therapy. *Intensive Care Med* 2013 Apr; 39(4): 558-68

³⁷ Wiedermann CJ, Joannidis M. Mortality after hydroxyethyl starch 130/0.4 infusion: an updated meta-analysis of randomized trials. *Swiss Med Wkly* 2012 Jul 30; 142: w13656

majority of experts considered that based on the small and limited available studies it is not possible to identify any subpopulation in which the benefit would outweigh the risks. Overall the expert group agreed that the benefit may exist in severe hypovolaemia in short duration only at the beginning i.e. perioperative setting and disappearing faster with patient's stabilisation. The experts suggested that benefits of HES may be seen in perioperative bleeding. The expert group unanimously agreed that the increased risk of renal events and the increased mortality observed in patients with sepsis and the critically ill could not be directly extrapolated to perioperative setting or trauma or to any other clinical setting. The experts agreed that the data available is not convincing however may suggest that the risks are lower in other settings than sepsis and critically ill patients. The experts highlighted that the administration of HES to normovolaemic patients in certain trials was potentially an important issue. The experts further highlighted that additional research on HES must be undertaken.

Finally the PRAC considered the data presented by the MAHs during the oral explanation held on 7 October 2013.

Overall risk-benefit conclusion

In view of the grounds for re-examination submitted by the MAHs, the PRAC took into consideration only the data available at the time of the previous recommendation in June 2013. This included recently published large clinical trials in critically ill patients and patients with sepsis, several meta-analyses as well as results of two unpublished clinical trials which compared HES with crystalloids and other colloids. The PRAC also consulted the views of experts through Ad-Hoc Expert meetings.

The PRAC considered that the use of HES for solutions for infusion has been shown to be associated with an increased risk of mortality and renal replacement therapy or renal failure. HES is also associated with other serious adverse reactions such as increased bleeding, hepatic organ failure, anaphylactic reactions and pruritus. For subjects with severe sepsis or septic shock the risks of increased mortality (and more frequent use of RRT) are considered to outweigh the limited benefits of more rapid attainment of haemodynamic stability compared to crystalloids. Furthermore, sufficient evidence is not available for this procedure to indicate that use in other indications outweighs the risks.

In view of the available data, the PRAC concluded that the benefit risk balance of hydroxyethyl starch solutions for infusion is not favourable in the approved indications and in any patient population. These conclusions are without prejudice to the conclusions of the referral under Article 107i of Directive 2001/83/EC that was conducted separately but in parallel. In the procedure under Article 107i of Directive 2001/83/EC additional data has been included that was not available when the PRAC issued its recommendation on the referral in accordance with Article 31 of Directive 2001/83/EC in June 2013 and therefore could not be considered in the re-examination of the latter in October 2013.

5. Communication plan

The PRAC considered that a Direct Healthcare Professional Communication (DHPC) was needed to communicate on the review of hydroxyethyl starch and the recommended regulatory measures. The communication should take due account of the conclusions of the procedure under article 107i, where additional data was considered.

6. Conclusion and grounds for the recommendation

Whereas,

- The Pharmacovigilance Risk Assessment Committee considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, for hydroxyethyl starch containing products for solutions for infusion (see Annex I).

- The Pharmacovigilance Risk Assessment Committee considered the data available for hydroxyethyl starch containing products for solutions for infusion in relation to the risk of mortality and renal failure. This included data from clinical studies and meta-analyses and Marketing Authorisation Holder's responses.
- The Pharmacovigilance Risk Assessment Committee considered that the use of hydroxyethyl starch is associated with an increased risk of mortality and renal replacement therapy or renal failure as well as other serious adverse reactions.
- The Pharmacovigilance Risk Assessment Committee therefore concluded, in view of the available data, that the increased risk of mortality and renal replacement therapy or renal failure associated with the use of hydroxyethyl starch containing medicinal products for solutions for infusion outweighs its limited clinical benefits in the approved indications and in any patient population.

The Pharmacovigilance Risk Assessment Committee, as a consequence, concluded that pursuant to Article 116 of Directive 2001/83/EC the benefit-risk balance for hydroxyethyl starch containing products for solutions for infusion is not favourable.

Therefore, in accordance with Articles 31 and 32 of Directive 2001/83/EC, the Pharmacovigilance Risk Assessment Committee maintains, by majority, its recommendation and consequently the marketing authorisations for all medicinal products referred to in Annex I should be suspended. These conclusions are without prejudice to the conclusions of the procedure under Article 107i of Directive 2001/83/EC. In the procedure under Article 107i of Directive 2001/83/EC additional data has been included that was not available when the PRAC issued its recommendation on the referral in accordance with Article 31 of Directive 2001/83/EC in June 2013 and therefore could not be considered in the re-examination of the latter in October 2013.

Appendix 1

Divergent positions to PRAC recommendation

Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-31/1348

Solutions for infusion containing hydroxyethyl starch

Divergent statement

The following members of PRAC did not agree with the PRAC's Recommendation on the Article 31 referral re-examination resulting from pharmacovigilance data for solutions for infusion containing hydroxyethyl starch based on the following reasons:

1. The results indicating harm in patients with severe sepsis may not be extrapolated to other patient groups and indications:
 - a. The expert group unanimously agreed that the increased risks of renal events and the increased mortality observed in patients with sepsis and the critically ill cannot be directly extrapolated to perioperative setting or trauma setting or to any other clinical setting
 - b. In sepsis the most important pathophysiological mechanism behind hypovolemia is a severe generalised inflammatory activation with vasodilatation and capillary leakage. In elective surgery and trauma the main mechanism is mostly a direct loss of blood volume, with an inflammatory activation of substantially lower magnitude and consequently substantially less capillary leakage.
 - c. In sepsis no clinical meaningful volume-sparing effect is seen while in elective surgery there is a clinically meaningful volume-sparing effect.
 - d. The relative increase in mortality risk is substantially lower in critically ill patients in general (CHEST study) compared to the studies on severe sepsis, suggesting potential effect-modification by patient subset.
2. Treatment of hypovolemia is symptomatic, aiming to resolve the immediate threat to life and vital organ function. The patients underlying condition (such as severe infection, trauma, reason for surgery) is, however, the main determinant for long-term survival. Improvement in short-term hemodynamic end-points is therefore clinically relevant and should contribute to the benefit-risk assessment.
3. Benefit in elective surgery in terms of volume-sparing effect and hemodynamic endpoints has been shown. Harm as identified in septic patients cannot be extrapolated to elective surgical patients. The benefit-risk relation in elective surgery is therefore considered favourable based on currently available data.
4. In trauma patients there is a rationale for colloids in specific settings, but limited data on clinical benefit. HES is still present in recently updated European guidelines on management of bleeding following major trauma. The benefit-risk relation in trauma is therefore considered favourable based on currently available data despite the uncertainty.
5. Alternative synthetic colloids (albumin and gelatin) are notably less well studied and there are data suggesting that they may not be considered as better alternatives. Albumin has possibly unfavourable outcome for some patient categories. Therefore, switching to alternative synthetic colloid therapy is a concern.
6. Additional measures should be proposed to further minimize the identified and potential risks.

Due to the above mentioned arguments the below mentioned PRAC delegates consider the benefit/risk balance of Hydroxyethyl starch (HES) positive for specified subgroups justifying the maintenance of the marketing authorisations of all HES-containing medicinal products subject to variation and conditions to the marketing authorisations.

PRAC members expressing a divergent position:

Jane Ahlqvist Rastad	10 October 2013	Signature:
Margarida Guimarães (PT)	10 October 2013	Signature:
Jolanta Gulbinovic (LT)	10 October 2013	Signature:
Herve Le Louet	10 October 2013	Signature:
Eva Jirsovà (CZ)	10 October 2013	Signature:
Tatiana Magálová (SK)	10 October 2013	Signature:
Isabelle Robine (FR)	10 October 2013	Signature:
Maia Uusküla (ET)	10 October 2013	Signature:
Qun-Ying Yue (SE)	10 October 2013	Signature:
Andis Lacis (LV)	10 October 2013	Signature:

Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-31/1348

Solutions for infusion containing hydroxyethyl starch

Divergent statement

The following member of PRAC did not agree with the PRAC's Recommendation on the Article 31 referral resulting from pharmacovigilance data for solutions for infusion containing hydroxyethyl starch based on the following reasons:

1. Treatment of hypovolemia is symptomatic, aiming to resolve the immediate threat to life and vital organ function. The patients underlying condition (such as severe infection, trauma, reason for surgery) is, however, the main determinant for long-term survival. Improvement in short-term hemodynamic end-points is clinically relevant and should contribute to the benefit-risk assessment. The benefit-risk in elective surgery can be considered favourable based on available data. In this indication HES can be acceptable for short term use.

2. Additional measures should be proposed to further minimize the identified and potential risks.

Due to the above mentioned arguments the below mentioned PRAC delegates consider the benefit/risk balance of Hydroxyethyl starch (HES) positive for specified subgroups justifying the maintenance of the marketing authorisations of all HES-containing medicinal products subject to variation and conditions to the marketing authorisations.

PRAC members expressing a divergent position:

Sabine Straus (NL)	10 October 2013	Signature:
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