**Disclaimer :**

This assessment report was provided by the United Kingdom Competent Authority at the time of the initiation of the procedure. It provides background scientific information which complements the final notification request sent by the United Kingdom Competent Authority for an EU review.

It should be understood that this assessment report reflects the position of the United Kingdom Competent Authority at the time of the initiation of the referral procedure and is without prejudice to any future position to be established on the matter by the European Medicines Agency through its Scientific Committees.

| |
|---|
| **Title of paper:** Hydroxyethyl starches Benefit / Risk review |

| | |
|---|---|
| **Product:**<br>Venofundin 6% (PL 03551/0097), Tetraspan 6% (PL 03551/0106) and Tetraspan 10% (PL 03551/0107); Hyperhaes (PL 08828/0157), Volulyte 6% (PL 08828/0174), Voluven 6% (PL 08828/0145) and Voluven 10% (PL 08828/0207); Plasma Volume Redibag 6% (PL 00116/0635) | **MAHs:**<br>B Braun Melsungen AG, Fresenius Kabi Ltd, Baxter Healthcare Ltd |
| **Active constituent:**<br>Hydroxyethyl starch | **Pharmaceutical form and route of administration**:<br>Artificial colloid in crystalloid carrier solution for intravenous administration |
| **Therapeutic classification:**<br>Plasma substitutes and plasma protein fractions<br>**ATC code:**<br>B05A A07 | **Legal status:**<br>POM |

# 1 BACKGROUND

Hydroxyethyl starches (HES) are synthetic colloids used for plasma volume expansion. HES formulations are classified according to their concentration, molecular weight (MW), and degree of molar substitution (MS). Recently published data has called into question the balance of risks and benefits of HES product.

# 2 DATA FOR CONSIDERATION

**Safety – published data**
Two large recently published trials investigating the safety of HES in critically ill patients compared HES with crystalloid; the Scandinavian Starch for Severe Sepsis/ Septic Shock (6S) (Perner 2012) and Crystalloid versus Hydroxyethyl Starch Trial (CHEST) (Myburgh 2012)

The 6S trial reported a significantly higher mortality at day 90 for the HES group: 51% (201/398) of the patients in the HES group versus 43% (172/400) in the crystalloid group died (Relative Risk (RR) 1.17; 95% Confidence Interval (CI) 1.01 to 1.36; P= 0.03). 6S also reported an increased requirement for renal replacement therapy (RRT) at 90 days after randomisation.

The results of CHEST showed an increased risk of renal dysfunction requiring renal replacement therapy in critically ill patients, including a large subgroup with sepsis. Renal replacement therapy (RRT) was used in 7.0% in the HES and 5.8% in the crystalloid group (RR= 1.21; 95% CI 1.00 - 1.45; p= 0.04). Renal injury occurred in 34.6% and 38.0% of patients in the HES and crystalloid groups (p = 0.005) and renal failure occurred in 10.4% and 9.2% of patients respectively (p= 0.12). The difference in 90 day mortality between HES and crystalloids in CHEST did not reach statistical significance either in the groups as a whole, or in the subgroup of approximately 1900 patients with sepsis. The patients in this study were at lower risk of death than those in 6S.

Another large randomised trial from 2008, the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study (Brunkhorst 2008) previously showed similar results to 6S, with increased mortality and renal dysfunction associated with HES compared with crystalloid in a population of patients with severe sepsis. In addition, three meta-analyses were published in 2013, which reviewed the published data (Haase 2013; Perel 2013; Zarychanski 2013).

The data on the use of HES in the treatment of burns patients are limited. Data from well-designed clinical studies with sufficient follow-up time are not available.

The FIRST (Fluids in Resuscitation of Severe Trauma) trial (James 2011) compared HES with crystalloid in resuscitation of patients with severe trauma, separated into blunt and penetrating trauma. A number of secondary endpoints were measured in FIRST, including biochemical and haemodynamic data. HES provided better lactate clearance and less renal injury than crystalloid for patients with penetrating trauma. No advantage was seen in patients with penetrating trauma. Significantly more blood and blood products during resuscitation were needed in the HES group and a significantly greater deterioration in coagulation measures was seen, although this could be due to differences in severity of injury. There was no difference between any groups in time to recovery of bowel function or mortality.

**Efficacy**

HES solutions for infusion are currently authorised in the setting of hypovolaemia to expand plasma volume. Colloidal solutions are used to sustain intravascular oncotic pressure and to shorten circulatory stabilisation time.

In the CHEST study in critically ill patients there was no significant difference in death rates between the HES group and the saline group and there was no clinically meaningful volume sparing effect of HES.

In sepsis patients the three recent published clinical trials (6S trial, CRYSTMAS trial, VISEP study) did not demonstrate any benefits of HES over comparators. Further data provided by the MAH is discussed below.

The meta-analysis by Zarychanski et al. (2013) found no evidence of benefit for HES over comparators in trials including trauma patients.

Benefits for elective surgical patients have been seen in short-term surrogate haemodynamic outcomes in a review of randomised clinical trials of 130/0.4 HES in resuscitation (Hartog 2011). The review included 56 trials, of which 45 were in the elective surgery setting. Findings favourable to HES 130/0.4 compared with crystalloid include higher cardiac output and less frequent hypotension measured by blood pressure in pre-load spinal anaesthesia. A modest volume sparing effect was also reported in this review, with 1.8 times as much crystalloid needed as HES in elective surgery. Haemodynamic benefits have also been reported in a randomised trial in patients with primary ovarian cancer (n=48) undergoing cytoreductive surgery compared HES 130/0.4 with crystalloid (Feldheiser 2012). Less study fluid was required in the HES group (p=0.049), and there was a longer intravascular effect and a reduced need for transfusion of fresh frozen plasma during surgery. Better haemodynamic stability, higher stroke volume, cardiac index, corrected flow time, and lower systemic vascular resistance were also seen in the HES group**.**

The trials in elective surgery are generally in small numbers of patients and without sufficient length of follow-up to allow conclusions on mortality or renal injury. Some additional data have been provided by Fresenius Kabi. Their meta-analysis of trials in cardiovascular surgery is described further below.

**Data provided by the MAH**

**MAH meta-analysis of trials in cardiovascular surgery**

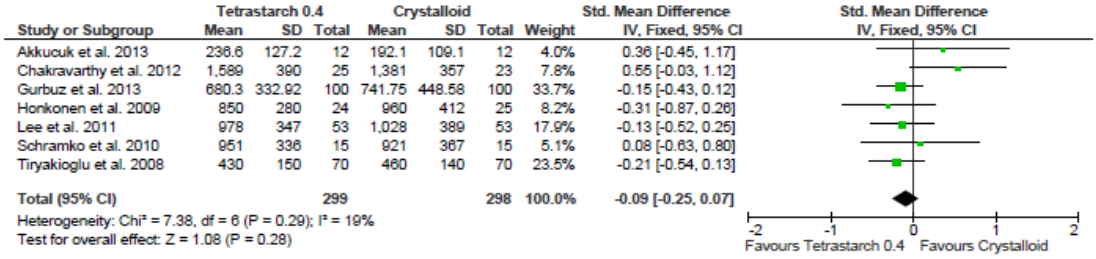
Fresenius Kabi provided a meta-analysis of trials in cardiovascular surgery comparing hydroxyethyl starches for volume expansion with alternatives, albumin, crystalloids and gelatine. Endpoints evaluated were total blood loss, frequency of transfusions, reoperation, kidney injury, mortality. Analysis of trial results was carried out separately for HES products of different molecular weights. Findings from the meta-analysis with respect to comparisons of HES 0.4/130 and crystalloid where statistical comparisons were possible are presented below. The clinical relevance of any differences observed in HES and crystalloid comparisons is questionable, and the data on the key safety endpoints of kidney injury and mortality are limited by the small number of events reported.

**Total blood loss: Tetrastarch (HES 0.4/130) versus crystalloid**

Total blood loss refers to intraoperative blood loss and blood loss up to 24 hours after the end of the operation. If data were not available for the complete time interval the largest available interval was selected for analysis. Units of blood loss were millilitres (ml). The standardized mean difference of the mean for the tetrastarch group minus the mean for the crystalloid

group was used as effect size. A fixed effect model was applied to calculate a common estimate using the inverse variance method. The estimated difference in blood loss between HES and crystalloid from the seven trials analysed was -0.09 ml, in favour of HES (95% CI -0.25 – 0.07). This was not statistically significant. The results are shown below in table 1.

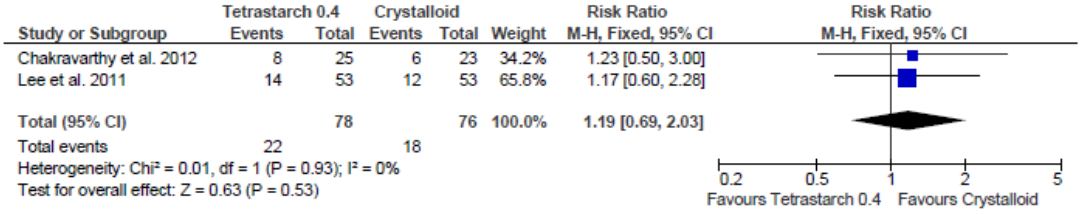
**Table 1: Total blood loss for HES (molar substitution 0.4, molecular weight 130 kD) versus crystalloid**




**Frequency of blood transfusions**

The number of patients receiving blood transfusions (event) is defined by the number of patients receiving intraoperative blood transfusions or transfusions up to 24 hours after the end of operation. If data were not available for the complete time interval the largest available interval was selected for analysis. The risk ratio was used as effect size (transfusion risk for the tetrastarch group divided by transfusion risk for the crystalloid group). Fixed effect models were applied to calculate a common estimate using the Mantel-Haenszel approach. The risk ratio for frequency of blood transfusions between HES and crystalloid from the two trials analysed was 1.19 (95% CI 0.69 – 2.03). The results are shown below in table 2.

**Table 2: Frequency of blood transfusions for HES (molar substitution 0.4, molecular weight 130 kD) versus crystalloid**




There is a lack of detail in the MAH analysis with respect to the size and length of follow up of the trials. The data on endpoints for harm are very limited. Only three studies comparing HES and crystalloid reported any events of acute kidney injury, and the criteria used for reporting these events where different in all three studies. The low numbers of events of kidney injury or mortality observed in direct comparisons of HES with crystalloid may reflect the short length of follow up and/or small trial size. It is not clear how much patient follow up was included in these studies; it is unlikely that long-term follow up to 90 days was carried out. Very few events of re-operations and mortality were observed, and therefore no conclusions can be drawn regarding these endpoints.

This meta-analysis, which is of limited methodological quality, does not show any advantage for HES over crystalloid in cardiovascular surgery, and does not provide any reassurance that the harms seen in the sepsis and intensive care population are not present in these patients.

**BaSES trial**

This was a randomised trial comparing 6% HES and isotonic saline in patients with sepsis (n=241) (completed May 2011, unpublished). The treatment protocol compared isotonic saline with alternating HES and isotonic saline administration. The primary endpoints were length of ICU stay and total hospital stay. The trial was powered to detect a 1 day difference in the length of hospital stay. A secondary endpoint was 30-day mortality. There was a statistically significant 8 day difference in the total length of hospital stay, in favour of the alternating HES/isotonic saline treatment regime (20.0 days vs 28.5 days). There was a difference of around 1 day in length of ICU stay in favour of alternating HES/isotonic saline, although the confidence intervals on the estimates of ICU stay length were very large. No increased mortality rate was seen, but the study was not powered to detect a difference such as seen in larger studies, and also had a shorter follow-up period. No statistically significant volume sparing effect was seen alternating HES/isotonic saline, and fluid balance was the same in both treatment arms. The time taken to reach haemodynamic endpoints was not measured. The isotonic saline treatment arm was noted to have an higher proportion of patients admitted with pneumonia (38% vs 28%, p=0.10), which could influence the length of patient stay, as these patients are at greater risk of pulmonary oedema occurring as a result of fluid resuscitation.

The patients who received HES in BaSES were treated with alternating HES and crystalloid. This treatment protocol is not used in any other of key studies considered in the referral. There shorter duration of follow-up also means the results are not directly comparable with those from 6S, CHEST, and VISEP.

**CRISTAL study**

The CRISTAL study (Colloids Compared to Crystalloids in Fluid Resuscitation of Critically Ill Patients: A Multinational Randomised Controlled Trial) is a clinical trial in 2857 patients including sepsis and trauma patients. The design compares two treatment arms, colloid and crystalloid. A variety of colloids and crystalloid treatments are included in the two treatment arms. The results have not yet been published, and the details of breakdown of the patients by treatment allocation and numbers of reported events were not presented. The findings include reduced 90-day mortality in the colloid group and no significant differences in renal function or need for RRT.

**UK Spontaneous reporting data**

There have been 45 reports of suspected adverse reactions to HES products in the UK. Three of these have been fatal. There have been 3 reports of renal dysfunction associated with HES, including one fatal case of renal failure.

**Clinical Guidelines**

The updated Surviving Sepsis Campaign (SSC) Guideline (Dellinger 2013) recommends that crystalloid should be the initial fluid of choice in the resuscitation of severe sepsis and septic shock. The updated SSC Guideline also recommends against the use of HES for fluid resuscitation of severe sepsis and septic shock, and suggests that albumin should be used for fluid resuscitation when patients require substantial amounts of crystalloids.

In a position statement on 16th June 2013, the Faculty of Intensive Care Medicine and the Royal College of Anaesthetists issued statements emphasising the international recommendations to use crystalloid solutions for fluid resuscitation. The statements note that albumin may be used in patients with severe sepsis who require large volumes of crystalloid.

**Usage data**

There is significant usage of HES products in the UK. In 2012, 443,991 500ml units of HES products were used in the UK. There is also significant usage in many other member states.

Number of 500ml units dispensed in UK hospitals per calendar year in the UK (Data from MIDAS)

| | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|
| **Hydroxyethyl starch products** | 548,441 | 591,269 | 624,920 | 592,795 | 443,991 |

# 3 DISCUSSION

The safety of HES in critically ill patients has been evaluated in published data from large randomised controlled trials, reporting findings of increased renal dysfunction in critically ill patients and patient with sepsis, and increased mortality in the severe sepsis population.

Three meta-analyses published in 2013 show increased 90-day mortality in patients who received fluid resuscitation with HES, compared with crystalloids. The magnitude of the relative risk for death is approximately 1.1 in all three meta-analyses, due to the impact of the most recently published data from CHEST and 6S, which are the two largest trials and make by far the greatest contribution to the total weight of meta-analysis. The meta-analyses which evaluated renal outcomes also reported increased use of renal replacement therapy (RRT) and increased risk of renal failure with HES compared with crystalloid treatment (Haase 2013; Zarychanski 2013). The strongest evidence for the increased risk of mortality is provided by data from patients with sepsis, as the 6S and VISEP trials were conducted in patients with severe sepsis, and CHEST included a large sub-population of patients with sepsis.

In the setting of burn injury, there are pathophysiological similarities between sepsis and early burn injury physiology with a massive inflammatory response and capillary leakage. There are insufficient data to show a clinical benefit for the use of HES compared with crystalloids in burns, and therefore use in this indication cannot presently be justified.

In the meta-analysis including a subgroup analysis of trauma patients (Zarychanski 2013) there was no signal of benefit, if anything there appeared to be an increase in mortality associated with HES, however the estimate has limited precision due to the relatively low number of events. The positive effect of HES in penetrating trauma patients reported in FIRST needs further confirmation, because the study is quite small. In trauma there may be a particular need for rapid volume expansion due to massive bleeding and the trauma population is highly heterogeneous, but evidence for benefit of HES in this setting is poor, and overall there is some concern of potential harm.

A possible rationale for why the harmful effects from HES seen in septic patients may not be generalised to all other indications and patient subsets is on the basis of possible pathophysiological differences between elective surgery patients and those with sepsis, in terms of increased capillary permeability due to a systemic inflammatory response. There is evidence that a Systemic Inflammatory Response (SIR), seen as part of sepsis may also occur in the absence of infection (Laffey 2002), and is part of postoperative physiology (Bone 1992). Systemic capillary leak is an early feature of the inflammatory response to injury (Gosling 1999), and is a potential mechanism for renal dysfunction via HES deposition in the kidneys.

Benefit for elective surgical patients has been shown in short-term surrogate haemodynamic outcomes along with a modest volume sparing effect, with 1.8 times as much crystalloid needed as HES in elective surgery (Hartog 2011), compared with no clinically relevant volume-sparing effect in sepsis and critical illness. It should be noted that the majority of the

trials in the review by Hartog et al. used older HES products, gelatins or dextrans as comparators; only 19 trials out of the 56 trials included in this review had a crystalloid comparator. In addition, the authors note that the studies were small, with a median sample size of 25 patients in the intervention group and 29 patients in the control group, and of short duration (median length 12 hours). The studies in elective surgery are not sufficiently large or long term to allow conclusions on the effect on mortality or renal function. Without adequately designed studies, an increased risk of increased mortality or renal dysfunction relative to crystalloids in the elective surgery population cannot be excluded.

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 in patients with sepsis and the critically ill. A key consideration with respect to the overall benefit-risk balance for HES is whether the harms observed in patients with sepsis could be extrapolated to other patient groups. Evidence for renal injury is a safety signal relevant for all clinical settings in which patients experience hypovolaemia requiring treatment 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.

# 4 CONCLUSIONS

1) On the basis of evidence from randomised controlled clinical trials, the use of hydroxyethyl starch, when compared to crystalloids, is associated with an increased risk of mortality and renal replacement therapy or renal failure as well as other serious adverse reactions in patients with sepsis and in the critically ill.

2) There is a lack of evidence to provide reassurance that these risks are not present in other clinical settings. Given that other patient populations such as burn injury, trauma and elective surgery patients may experience a systemic inflammatory response comparable to critically ill or septic patients, a similar risk may apply to these populations. In addition, it is possible that some patients in the above categories may go on to develop critical illness or sepsis and therefore may be harmed by the prior administration of hydroxyethyl starch.

3) There is little evidence that hydroxyethyl starch provides any clinical benefit over crystalloids in any setting. Taking into consideration the limited evidence for benefit, and the increased risk of mortality and renal injury in septic patients and those that are critically ill, it is not possible to identify a patient population where the benefits of treatment outweigh the risk. Therefore, suspension of the marketing authorisations for hydroxyethyl starch products in all patient populations is considered necessary to protect public health.

# 5 REFERENCES


Basel Starch Evaluation in Sepsis (BaSES). Last verified August 2011. http://clinicaltrials.gov/ct2/show/NCT00273728.

Bone, RC et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest. 1992; 01:1644-55.

Brunkhorst F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. NEJM. 2008; 358: 125 -39

Dellinger RP, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013; 41:580–637

Feldheiser AV, et al. Balanced crystalloid compared with balanced colloid solution using a goal-directed haemodynamic algorithm. Br J Anaesth. 2012; 110 (2): 231-40.

Gosling, P. Prevention of post-traumatic clinical capillary leak syndrome. Trauma. 1999; 1: 91-103.

Haase N, 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. BMJ. 2013 Feb 15;346:f839

Hartog CS, et al. A systematic review of third-generation hydroxyethyl starch (HES 130/0.4) in resuscitation: Safety not adequately addressed. Anesth Analg. 2011;112:635-45.

James, MFM 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). British Journal of Anaesthesia. 2011; 5:693-702.

Laffey, JG et al. The systemic inflammatory response to cardiac surgery. Anesthesiology 2002. 97; 2015-52.

Myburgh J, et al. Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care. Published on 17 October 2012 at NEJM.org.

Perel P, et al. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Sys Rev. 2013 Feb 28;2:CD000567

Perner A, et al. Hydroxyethyl starch 130/0.4 versus Ringer's acetate in severe sepsis. NEJM. 2012; 367: 124-134

Zarychanski R, et al. 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 Feb 20;309(7):678-88