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Assessment report for solutions for infusion containing hydroxyethyl starch

Procedure under Article 107i of Directive 2001/83/EC

Procedure number: EMEA/H/A-107i/1376

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 27 June 2013, the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) notified the Member States, European Medicines Agency and the European Commission in accordance with Article 107i of Directive 2001/83/EC, of its consideration of the need to suspend the marketing authorisations for Hydroxyethyl starch (HES) solutions for infusion in the UK.

The decision of the MHRA was based on evidence from randomised controlled clinical trials where HES solutions for infusion, when compared to crystalloids, were associated with an increased risk of mortality and renal replacement therapy (RRT) or renal failure as well as other serious adverse reactions in patients with sepsis and in the critically ill. The MHRA considered there is a lack of evidence to provide reassurance that these risks are not present in other clinical settings and there is little evidence that HES provides clinical benefit over crystalloids in any setting. Therefore, given the evidence for harm associated with HES products and the continued significant use of these products, the MHRA considered the need of urgent national action.

The PRAC was requested to assess the matter and to make a recommendation under the provisions of Article 107i of Directive 2001/83/EC to the Human Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMDh) on any measures necessary to ensure the safe and effective use, and on whether the marketing authorisation for these products should be maintained, varied, suspended or withdrawn.

After reviewing all the available data submitted by the Marketing Authorisation Holders (MAHs) and by others Stakeholders, the PRAC adopted a recommendation on 10 October 2013.

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). 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.

Concerns with regards to HES were previously considered by the Pharmacovigilance Working Party in September 2008 and by the PRAC in November 2012 on the basis of results of several studies, some of which showed an increased risk for 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 in intensive care unit (ICU) patients (CHEST³). 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.

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) had recommended in June 2013 that HES solutions for infusion be suspended in the European Union (EU), following an assessment of

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

available data which concluded that their benefits do not outweigh the risks of RRT or acute renal failure and mortality. A number of marketing-authorisation holders exercised their legal right to request a re-examination of the recommendation, and this procedure was considered by the PRAC separately.

In the meantime, on 27 June 2013 the UK's MHRA initiated an urgent union procedure under Article 107i of Directive 2001/83/EC, following its consideration of the need to suspend the marketing authorisations for HES solutions for infusion in the UK. This review procedure ran separately but in parallel with the re-examination of the PRAC's June 2013 Article 31 of Directive 2001/83/EC recommendation. In the scope of the Article 107i of Directive 2001/83/EC, new data which were not available in the referral under Article 31 of Directive 2001/83/EC were considered.

2.1. Clinical aspects

2.1.1. Clinical safety

In support of the clinical safety of HES solutions for infusion, published data on the risks of mortality and renal injury associated with HES solutions for infusion, in critically ill and ICU patients (including sepsis, trauma, surgical and non-surgical ICU patients) and surgical patients were provided. These data included those previously considered by the PRAC as part of the assessment of the Article 31 referral. It also included new available data including randomised clinical studies, meta-analysis of clinical studies, post-marketing experience, responses submitted by the marketing authorisation holders (MAHs) in writing and at oral explanations on the safety and efficacy of hydroxyethyl starch containing products for solutions for infusion, as well as stakeholder submissions in particular with regards to the risk of mortality and renal failure. Only a summary of relevant data is presented hereafter⁴.

VISEP, 6S and CHEST trials limitations

The PRAC previously considered the VISEP, 6S and CHEST trials and acknowledged the limitations of the studies in the context of the referral under Article 31 of Directive 2001/83/EC. Although some limitations were identified, the PRAC concluded that the studies were well-designed and adequately powered to show an increased risk of mortality (6S, VISEP) in patients with sepsis and a risk of renal replacement therapy or renal failure in patients with sepsis and those who were critically ill (6S, VISEP, CHEST). However, the MAHs further expressed concerns over the design and execution of the VISEP, 6S, and CHEST trials, and the possibility that this may have influenced the results and cast doubt on the strength of the evidence. The main points raised by the MAHs were patients starting study treatment several hours after admission to ICU and possibly being haemodynamically stable at randomisation; patients subsequently randomised to the crystalloid arm had received initial treatment with colloids; and that there was the lack of defined criteria for starting RRT in the protocols.

The PRAC has again carefully considered the arguments presented by the MAHs. As published in a letter to the editor of the *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine* (Chappell and Jacob), the authors of the 6S study state that the "*24 hour window from diagnosis of severe sepsis resembles clinical practice, where fluid resuscitation in septic patients is initiated without waiting for the results of new blood samples to confirm the diagnosis of severe sepsis*". Forty-nine percent (49%) of patients in 6S received colloids in the 24 hours prior to randomisation, "*but the*

⁴ This report details the assessment of the Article 107i of Directive 2001/83/EC procedure. Details on the assessment report for the Article 31 procedure that was conducted separately but in parallel to this procedure can be found in the respective report.

clinician judged that fluid resuscitation was still needed as this was an inclusion criterion". Therefore, the MAHs' suggestion that patients were already haemodynamically stable and no longer hypovolaemic at randomisation was not supported by the PRAC.

Regarding the observation that in some of the studies patients in the crystalloid group had already received colloids prior to randomisation, the PRAC highlighted that early exposure to HES would logically be expected to reduce the observed differences between the treatment arms, if it had any effect at all.

Although there was no trigger for starting and terminating RRT specified in the CHEST study protocol the suggestion that this could bias the results in favour of one intervention or another is not accepted, as the physicians were blinded to the treatment in CHEST and similarly in 6S.

According to the authors of the 6S study, kidney failure without RRT was not a 'clear' or 'absolute' contraindication for HES. It is important to note that the increased risk of death with HES was independent of kidney failure at inclusion in the pre-planned subgroup analysis.

Overall the concerns over the study design and execution of VISEP, 6S, and CHEST raised by the MAHs do not constitute major limitations of these studies, and do not alter the assessment of these data as robust evidence of increased renal dysfunction and mortality associated with the use of HES from large randomised clinical trials in septic and critically ill patients. Furthermore, the PRAC has previously considered and assessed these data as part of the referral procedure under Article 31 of Directive 2001/83/EC and these arguments did not alter the conclusion reached on the risks of renal injury and mortality associated with HES in sepsis and critically ill patients.

Risk of mortality

Safety data from clinical trials

- CRYSTAL trial⁵

The CRYSTAL trial results were already considered by the PRAC in the context of the referral procedure under Article 31 of Directive 2001/83/EC. However, the draft manuscript intended for publication and the protocol of this study was made available by the principal investigator to the PRAC in the context of the referral under Article 107i of Directive 2001/83/EC. These were not taken into consideration 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 also be considered in the re-examination of the latter in October 2013.

The results of the study are presented and discussed hereafter.

Protocol

The CRYSTAL study was an investigator-initiated study comparing colloid and crystalloid therapies for fluid resuscitation. It was a multinational, randomised, controlled parallel group trial. Patients included were those hospitalised in an ICU who needed fluid resuscitation according to the physician in charge of the patient, and were randomised to receive either crystalloids (0.9% saline, hypertonic saline or Ringer Lactate) or colloids (gelatins, starch solutions (including HES) and albumin).

Treatment was then chosen from whatever was available at local hospitals within this framework. According to the protocol, "*those patients whose physician believes they should receive colloids like albumin will receive them and not be part of the study.*"

⁵ Annane D. et al. CRISTAL: Colloids Compared to Crystalloids in Fluid Resuscitation of Critically Ill Patients: A Multinational Randomised Controlled Trial. NCT00318942. Available on: <http://clinicaltrials.gov/ct2/show/NCT00318942>

The study was not blinded as according to the protocol "*double blind seems unfeasible as the time window for inclusion is extremely short (treatment should be available promptly at bedside) and the amounts of volume replacement for all ICU stay could not be predicted a priori.*"

The primary endpoint was 28-day mortality rate. Eleven secondary endpoints were listed, first of which was 90-day mortality rate. All the secondary endpoints were subjective.

Block randomisation stratified by site and diagnosis, (1) trauma or haemorrhage, (2) sepsis, (3) other diagnoses was used.

A total of 2857 patients, 1414 in the colloids arm and 1443 in the crystalloids arm, were recruited over the nine years period of the study.

Prior to ICU admission, 585 and 685 patients in the colloids and crystalloids arms, respectively, received a median volume of 1000 ml of colloids [Interquartile range (IQR): 500-2000]; and 526 and 402 patients in the colloids and crystalloids arms, respectively, received a median volume of 950 ml of crystalloids [IQR: 500-1000].

Severe sepsis was the main diagnosis upon admission in both arms.

Results – Interim analyses

The study was stopped on the basis of 706 observed deaths from 2,612 enrolled patients before the end of the study. The boundaries of the sequential plan were drawn to demonstrate an absolute difference of 5% in 28-day mortality rate between the two treatment arms, assuming a 20% mortality rate in the crystalloids group, and with alpha and beta of 5% and 10% respectively. When a boundary is crossed, the enrolments in the study may be stopped, and the conclusion depends on which boundary has been crossed. The conclusion was that there was no statistical difference in 28-day mortality between those groups.

At Day 28, they were 359/1414 (25.4%) deaths in the colloids arm and 390/1443 (27.0%) in the crystalloids arm (RR =0.96; 95%CI: 0.88-1.04; P=0.26).

At Day 90, they were 434/1414 (30.7%) deaths in the colloids arm and 493/1443 (34.2%) in the crystalloids arm (RR =0.92; 95%CI: 0.86-0.99; P=0.03).

There was significant heterogeneity in mortality rates and treatment effect across centres.

Conclusion

The authors of the study concluded that "*among ICU patients with hypovolemia, the use of colloids vs crystalloids did not result in a significant difference in 28-day mortality. Although 90-day mortality was lower among patients receiving colloids, this finding should be considered exploratory and requires further study before reaching conclusions about efficacy.*"

The PRAC acknowledged a number of limitations of the study such as the fact that HES is only part of one of the arms and therefore the results are to be taken with caution. Other limitations included the possibility of excluding patients if their physicians considered them to need colloid therapy, which has an impact on the ability to generalise the results and the likelihood that there was a shift in clinical practice during the long duration of this pragmatic trial. The PRAC was of the opinion that the rationale for not blinding the study was clear and understandable.

The PRAC noted that protocol deviations occurred in both arms of the study. In the colloids arm, these included administration of normal saline 252/1414 (17.8%), Ringers lactate 88/1414 (6.2%), and hypertonic saline 19/1414 (1.3%). In the crystalloid arm, these included administration of gelatins 24/1443 (1.7%) and hydroxyethyl starch 69/1443 (4.8%). Although some limitations were highlighted

as described above, the PRAC noted that this randomised controlled trial favours colloids (including HES) for volume resuscitation due to lower volume needed, more ventilator- and vasopressors- free days. In addition, the PRAC noted that colloids (including HES) did not increase the risk of mortality at day-28 and day-90. The PRAC therefore acknowledged the results of this study which shows no risk of mortality associated with the use of HES but considered that given the limitations of this study its findings could not negate the findings from 6S and VISEP studies that had shown an increased risk of mortality in critically ill patients.

- BaSES⁶

The BaSES (Basel Starch Evaluation in Sepsis) trial results are further discussed hereafter.

Protocol

The purpose of this study was to determine whether initial infusion therapy with HES and Ringer's lactate in septic patients reduces ICU and hospital length of stay without impairment of renal function.

This trial was double-blind, randomised and included 241 patients with sepsis, severe sepsis and septic shock. Patients received 1000 ml study infusion (i.e. either HES 130/0.4 or saline) followed by 1000 ml Ringer's lactate, alternating these treatments up to a total volume of 50 ml/kg per day of study infusion in the first five days of intensive care treatment.

Primary outcome measures were ICU length of stay, hospital length of stay and mortality (ICU, hospital and one year). Secondary outcome measures were kidney function at ICU discharge and after one year, and lung function during ICU stay (see section "risk of renal injury").

In total, 241 patients (2 ICUs in one hospital) with sepsis were resuscitated with 6% HES 130/0.4 in saline or isotonic saline for 5 days.

Results and conclusion

The difference in ICU length of stay was nearly 24 hours in favour of HES, although this difference was not statistically significant. Total length of hospital stay was statistically significantly reduced with HES.

The RR (95% CI) for mortality did not differ between HES and saline (RR 0.97, 95% CI 0.65-1.45). No differences were found in mortality between the two groups.

The authors of the study concluded that with strict alternating intravenous application following a hemodynamic protocol, administration of 6%HES (130/0.4) results in no significant reduction of the amount of resuscitation fluid, and no increase in the risk of acute kidney injury (see section "risk of renal injury") or mortality, but did decrease ICU and hospital length of stay compared with Ringer's lactate.

The PRAC noted the small sample size of this study to detect an increased risk of mortality. A meta-analysis by Haase et al, 2013 which included the results from the BaSES found an increased risk of renal replacement therapy for HES compared with crystalloids.

⁶ Siegemund M. Firstly presented at European Society of Anaesthesiology conference 2012. Basel Study for Evaluation of Starch (130;0.4) Infusion in Septic Patients: BaSES (130;0.4) Trial, listed at <http://clinicaltrials.gov/show/NCT00273728>

Safety data from meta-analysis or analysis

- Wiedermann CJ and Joannidis M 2012⁷

Wiedermann CJ and Joannidis M 2012 published an updated version of a previous meta-analysis, with the FIRST⁸ and CRYSTMAS⁹ studies included as new additions. These two studies provide more than 50% of the weight in the analysis. Overall, 13 studies reporting 1,131 participants met the inclusion criteria.

The results showed a pooled RR for mortality of 1.14 (CI 0.89 to 1.46). However, publication bias favouring HES was detected ($p=0.038$), and after adjustment the RR for mortality was 1.25 (CI 0.98 to 1.58; $p=0.069$). No heterogeneity was found (I^2 , 0%; CI, 0% to 32%; $p = 0.81$).

The review of Wiedermann and Joannidis 2012 have shown that HES does not negatively affect mortality and renal function in surgical patients, although the observation periods were usually too short to provide longterm data on mortality.

- M.A.R.C.O meta-analysis

The meta-analysis of trials in surgical settings initiated by one of the MAHs and conducted by the clinical research organisation M.A.R.C.O, that had already been considered in the context of the referral under Article 31 of Directive 2001/83/EC, was provided.

The endpoints evaluated were total blood loss, frequency of transfusions, reoperation, kidney injury and mortality. Thirty-six (36) peer reviewed articles were considered in a period of 28 years. Studies examined lower and higher molecular weight (130 – 450) HES products with molecular substitution ratios between 0.4 – 0.7.

No statistically significant difference in mortality was identified for HES products relative to comparators (crystalloid, albumin, gelatin) in this analysis.

Table 1 - Mortality – Combined HES (0.4-0.7) vs. Combined Comparators

| | Combined HES | Combined Comparators |
|---|---------------------|-----------------------------|
| Mortality | 0.5% (6/1235) | 0.7% (9/1262) |
| Common Risk Ratio (HES over comparators) | 0.80; $p=0.65$ | |

The low numbers of events mortality observed in direct comparisons of HES with crystalloid may reflect the short length of follow up and/or small trial size. The PRAC noted that very few events of mortality were observed in the studies included and that the studies included in this meta-analysis had not been designed nor powered to investigate effects on mortality.

Safety data from an analysis: ARISCAT by Canet J *et al.* 2013¹⁰

The prospectively compiled database of the ARISCAT study of a large, representative cohort of general surgical patients was reanalysed to compare outcomes according to whether intraoperative colloids

⁷ 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

⁸ 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

⁹ 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; 16:R94

¹⁰ Canet J, Sabaté S, Mazo V. Effects of intraoperative colloid administration on outcome in a population-based general surgical cohort: a propensity score analysis. *Minerva Anestesiol.* 2013 Aug; 79(8):891-905. Epub 2013 May 6

were administered or not; a propensity score was used to adjust for potential confounders. The primary outcomes were major postoperative complications. Secondary outcomes were postoperative hospital-free days within 90 days and mortality at 30 and 90 days. In a retrospective survey each centre's data collectors were asked to estimate the proportions of the different colloids administered during the study period.

Of 2462 patients analysed, 556 (22.6%) received some type of colloid intraoperatively. The median (25th-75th percentile) of total fluids administered was significantly higher in patients receiving colloids (10.0 [6.9-14.1] mL·kg⁻¹·h⁻¹ vs. 8.8 [6.0-12.8] mL·kg⁻¹·h⁻¹ for patients not receiving colloids; P<0.01). The median volume of colloids administered was 7.5 (6.3-10.4) mL·kg⁻¹. An estimated 75.7% of the patients received third-generation hydroxyethyl starches (130/0.4). Patients receiving colloids had 1.9 fewer postoperative hospital-free days (P<0.006). There were no significant differences in 30- and 90-day mortality.

The PRAC acknowledged potential methodological limitations of this observational non-randomized study and that the results should be interpreted with caution.

- Zampieri FG *et al.* 2013¹¹

Zampieri FG *et al.* 2013 performed a retrospective observational analysis including 894 patients submitted to oncologic surgery. A total of 385 propensity-matched patients remained in the analysis: 97 in the no-hydroxyethyl starch group and 288 in the hydroxyethyl starch group. There were no differences between the groups in the need for other blood products, intensive care unit length of stay or mortality. The PRAC noted that this was a retrospective observational study and so heterogeneity and selection bias are limitations for this type of study.

Safety data from the Rational Fluid Therapy in Germany (RaFTinG) clinical registry¹²

One of the MAHs submitted the RaFTinG clinical registry summary report.

The RaFTinG clinical registry was a prospective non-interventional ICU registry including 65 German ICUs. In total, 4545 patients were documented in the presented data. In the analysis presented, the primary aim was to evaluate the impact of different colloids (HES 200, HES 130/0.4, HES 130/0.42, and gelatin) and crystalloids on 90-day mortality (defined as ICU stay plus 90 days after discharge) by Cox regression analysis. The impact of resuscitation fluid type on secondary endpoints of ICU mortality, renal replacement therapy, and acute kidney injury was evaluated by multiple logistic regression.

Conditions present at admission which might have had an influence on endpoint incidence were included in the regression model to adjust for imbalances of the cohorts. The following parameters were used for adjustment:

- Age
- Sex
- Mortality risk based on SAPS II and Apache II on admission
- Chronic renal failure on admission
- Sepsis on admission

¹¹ Zampieri FG, Ranzani OT, Morato PF, Campos PP, Caruso P. Effect of intraoperative HES 6% 130/0.4 on the need for blood transfusion after major oncologic surgery: a propensity-matched analysis. *Clinics (Sao Paulo)*. 2013 Apr;68(4): 501-509

¹² Rational Fluid Therapy in Germany (RaFTinG). Available on ClinicalTrials.gov (NCT01122277) last updated on 07 July 2011: <http://clinicaltrials.gov/ct2/show/NCT01122277?term=NCT01122277&rank=1>

- Cumulative units packed red blood cells*
- Cumulative fluid balance
- Average colloid/crystalloid dose/day*
- Standardised AUC of SOFA score*
- Vasopressor use > 0.6 mg/h

*until onset of event investigated

During ICU stay 54.6% of the study patients received only crystalloids and 45.4% received colloids. Patients in the colloid group had more severe illness on admission (as measured by SAPS II and APACHE II scores) and were more likely to have severe sepsis (69.1% for colloids group, 64.6% for crystalloids only). The cumulative fluid balance was comparable for patients treated with or without colloids. Packed red blood cell (PRBC) and non-PRBC transfusion were similar among patients treated with or without colloids.

Overall mortality for all patients was 9.6% on ICU and 16.0% for 90-day-mortality. Unadjusted ICU mortality was higher for patients treated with colloids compared with those treated with crystalloids only. Compared with crystalloids only the mortality risk was significantly higher for gelatin or HES 130/0.42 and HES 200 infusion. HES 130/0.4 infusion had no independent effect on ICU or 90-day mortality.

In sub-group analyses, the adjusted risks of ICU and 90-day mortality were analysed separately for surgical vs. medical patients and patients with or without severe sepsis on admission, respectively. Since HES 130/0.4 was the most commonly administered colloid (n=1142), subcohort analyses were only performed for patients who received HES 130/0.4 compared to those who solely received crystalloids. The adjusted risk of ICU mortality was similar for patients treated with HES 130/0.4 or solely crystalloids in the subcohort of patients with severe sepsis on admission. In the subcohort of patients admitted without severe sepsis, the adjusted risk of ICU mortality was lower for patients treated with HES 130/0.4 as compared to those receiving only crystalloids. For surgical patients, the adjusted risk of ICU mortality tended to be lower for patients treated with HES 130/0.4 as compared to solely crystalloids, whereas there was no difference in medical patients. This effect could not be observed for medical patients.

Therefore, the results presented from RaFTinG showed no statistically significant differences between patients treated with crystalloids only (n=2482) and those treated with colloids (all HES preparations and gelatin, n=2063) for the endpoints of 90-day mortality.

Non-significant trends favouring HES 130/0.4 were reported for ICU mortality (OR 0.858, 95% CI 0.560 – 1.315), and 90-day mortality (HR 0.873, 95 % CI 0.695 – 1.097). The numbers of patients included in this subgroup analysis for crystalloids only (n=1885) and HES 130/0.4 (n=1127) differ from the numbers of patients assessed for baseline characteristics; crystalloids only (n=2482), HES 130/0.4 (n=1142). The reason for exclusion of patients, including a large number of patients from the crystalloid only group, from the subgroup analysis is not apparent.

Differences favouring HES 130/0.4 are reported for ICU mortality when only surgical patients or only patients without severe sepsis are considered and renal failure according to RIFLE. Risk estimates and details of the numbers of patients included when surgical admission patients only or patients without severe sepsis on admission only are considered are not provided.

Overall the results from RaFTinG do not show an increased risk for the mortality in patients admitted to ICU receiving colloids compared with crystalloids only, or in a subgroup of ICU patients receiving

HES 130/0.4 compared with crystalloids only. The PRAC noted, however, that this was an observational study and only limited conclusions can be drawn with respect to relative benefits and risks of treatment as it is not possible to exclude that treatment bias or differences between baseline characteristics between the treated groups could have had an impact on the results.

Risk of renal injury

Safety data from clinical trials

- BaSES

The results of the BaSES trial showed no differences in incidences of acute kidney injury (AKI) and RRT between the two groups. No patients required RRT after one year (cited according to Haase *et al.* 2013). However, given the limited number of patients included in this study these results need further confirmation.

Safety data from prospective and retrospective observational studies

- Sümpelmann R *et al.* 2011 (PASS study)¹³

PASS is a European multicentre (11 centres in 5 countries) open prospective observational postauthorisation safety study to evaluate the use of HES 130/0.42/6:1 in normal saline (ns-HES, 629 children, 2006-2009) or in a balanced electrolyte solution (bal-HES, n=475) in 1130 children up to 12 years undergoing surgery. Data were collected prospectively using a standardised case report form. In roughly one third of patients, biochemical changes were also assessed.

Mean infused volume was approximately 10 (0.8-50) ml/kg. Mean duration of observation was short, 6 ± 14 (0.1– 216) hours. Sixty (60) adverse events (3.5%) were reported in 40 patients out of 1130. All cases resolved until the end of the study. Mild to moderate adverse drug reactions (hemodilution, abnormal acid-base balance, low blood pressure) were reported in 14 (1.2%) patients. No anaphylactoid reactions, clotting disorders or renal failure was observed. There were significantly fewer complications (adverse events (AE) and drug reactions (ADR)) with HES in balanced electrolyte solution. For the AE/ADR rates, dose-response but no age relationships could be demonstrated.

The authors concluded that PASS is an audit of international intraoperative anaesthesiological practice in children. They consider that this study where moderate doses (< 20 ml/kg) were used with adherence to the contraindications (hypervolemia, renal failure, intracranial bleeding, severe hyponatremia or hyperchloremia, hypersensitivity to HES, severely impaired hepatic function, and congestive cardiac failure) supports the safety of these solutions.

The PRAC acknowledged that HES was used in both study arms and therefore no conclusions on beneficial or harmful effects of HES can be drawn. However, the PRAC noted that no serious adverse events related to HES occurred during the surgery, which may provide some reassurance that serious adverse effects do not occur very commonly because if this were the case a higher number of these events could be expected to have been reported.

- Boussekey N *et al.* 2010¹⁴

This observational retrospective study included 363 patients hospitalised for more than 72 hours in an ICU. A hundred and sixty eight patients received HES during their stay and 195 did not. Patients'

¹³ Sümpelmann R, Kretz FJ, Luntzer R, de Leeuw TG, Mixa V, Gäbler R, Eich C, Hollmann MW, Osthaus WA. Hydroxyethyl starch 130/0.42/6:1 for perioperative plasma volume replacement in 1130 children: results of an European prospective multicenter observational postauthorization safety study (PASS). *Paediatr Anaesth.* 2012 Apr;22(4):371-8. Epub 2011 Dec 23

¹⁴ Boussekey N, Darmon R, Langlois J *et al.* Resuscitation with low volume hydroxyethylstarch 130 kDa/0.4 is not associated with acute kidney injury. *Crit Care.* 2010;14(2):R40. Epub 2010 Mar 18

baseline characteristics were recorded on admission and type and volume of fluid resuscitation during the first 3 weeks of ICU stay. Urine output, the risk of renal dysfunction, injury to the kidney, failure of kidney function, loss of kidney function and end-stage kidney disease (RIFLE) classification and sepsis related organ failure assessment (SOFA) score were documented over 3 weeks.

Patients in the HES group were more severely ill on admission but AKI incidence was similar (as well as ICU mortality). Urine output ($P = 0.74$), RIFLE classification ($P = 0.44$) and SOFA score ($P = 0.23$) was not different. However, HES volumes administered were low (763+/-593 ml during the first 48 hours).

As this is an observational retrospective study, the study has numerous biases. The HES group was more severely ill, the HES volumes administered were low, and attending physicians could have generated a systematic bias with no HES use when patients had renal failure or were at risk of AKI. In addition, the observational follow-up is short (21 days) and the number of patients included in the study is low. Moreover, the selection of these patients is unclear, but relevant selection bias cannot be ruled out as this constitutes only 45% of the initial population. Nonetheless, it is demonstrated that (contrary to similar kidney function), for example the frequency of hemofiltration (7% vs 0% and 8% vs 6% comparing HES to no-HES in patients with initially normal kidney function and RIFLE at risk) were numerically larger. However, this is not significantly different, given the relatively small numbers with consecutively low statistical power. The same applies to mortality and other clinically relevant outcomes. Overall, the data provided cannot exclude a risk of acute kidney injury.

The PRAC acknowledged the limitations of the study and considered that a new well-designed study should be performed.

Safety data from meta-analysis and retrospective chart review

- Martin *et al.* 2013¹⁵

The aim of this meta-analysis was to evaluate renal safety with the active substance of the latest generation of waxy maize-derived HES in surgical patients. The authors focused on prospective, randomised, controlled studies that documented clinically relevant variables with regard to renal effects of waxy maize-derived HES 130/0.40. Seventeen (17) studies that analysed patients ($n = 1,230$) undergoing a variety of surgical procedures were included.

For maximum serum creatinine values, the effect size estimate was 0.068 (95% CI: -0.227 to 0.362; $P = 0.65$). For calculated creatinine clearance values, pooled risk difference was 0.302 (95% CI: -0.098 to 0.703; $P = 0.14$). For incidence of acute renal failure, pooled risk difference was 0.0003 (95% CI: -0.018 to 0.019; $P = 0.98$). For incidence of renal replacement therapy, pooled risk difference was -0.003 (95% CI: -0.028 to 0.022; $P = 0.85$).

Therefore, the results showed no evidence for renal dysfunction caused by waxy-maize derived HES 130/0.4 in surgical patients. No significant difference for the effect of HES 130/0.4 on serum creatinine and no significant risk difference of acute renal failure as compared with respective controls, which included higher molecular weight HES 200, gelatin, human albumin, and crystalloid solutions were found. The PRAC noted that a limitation of this meta-analysis was that only 6 of the studies directly compared HES with crystalloids.

- Endo *et al.* 2012¹⁶

Endo *et al.* conducted an uncontrolled retrospective chart review to identify adult surgical patients with intraoperative blood loss of ≥ 1000 mL at a university hospital. AKI was defined as $>50\%$ increase in

¹⁵ Martin C, Jacob M, Vicaut E, et al. Effect of waxy maize-derived hydroxyethyl starch 130/0.4 on renal function in surgical patients. *Anesthesiology* 2013; 118(2):387-94

¹⁶ Endo A, Uchino S, Iwai K, Saito K, Sanui M, Takinami M, Uezono S. Intraoperative hydroxyethyl starch 70/0.5 is not related to acute kidney injury in surgical patients: retrospective cohort study. *Anesth Analg.* 2012 Dec; 115(6):1309-14

serum creatinine from the preoperative value within 7 days after the operation according to the RIFLE (Risk, Injury, Failure, Loss, or End-stage kidney disease) criteria. The study compared the incidence of AKI between patients with and without intraoperative HES administration. Multivariate logistic regression analysis and propensity score matching were also conducted to elucidate the impact of HES on postoperative AKI.

Among 14,332 surgical cases, 846 patients met the inclusion criteria. In patients given HES (a median dose of 1000 mL, n = 635), 12.9% developed AKI, compared with 16.6% (odds ratio: -3.7%, 95% CI: -1.7% to 9.1%) in patients without HES (n = 211). Multivariate logistic regression analysis showed that HES was not an independent risk factor for postoperative AKI (odds ratio: 0.76, 95% CI 0.48-1.21). Using the propensity score, 179 pairs were matched. In patients with HES, 12.3% developed AKI, compared with 14.5% in patients without HES (odds ratio: -2.2%, 95% CI: -4.9% to 9.3%).

The authors concluded that intraoperative 6% HES 70/0.5 in a low dose was not related to postoperative AKI in patients with major intraoperative blood loss. They however highlighted that randomised controlled trials are warranted to further evaluate the safety and efficacy of low-molecular-weight HES. The PRAC noted that this study had similar shortcomings to those of the study by Zampieri *et al.* 2013.

- Mutter TC *et al.* (2013)¹⁷

The latest Cochrane review by Mutter *et al.* 2013 focused on effects on kidney function of HES versus other fluid therapies in different patient populations.

Randomised controlled trials and quasi-RCTs in which HES was compared to an alternate fluid therapy for the prevention or treatment of effective intravascular volume depletion were included. Primary outcomes were renal replacement therapy (RRT), author-defined kidney failure and AKI as defined by the RIFLE criteria.

This review included 42 studies (11,399 patients) including 19 studies from the original review (2010), as well as 23 new studies. Fifteen studies were excluded from the original review (nine retracted from publication due to concerns about integrity of data and six lacking individual patient creatinine data for the calculation of RIFLE criteria). Overall, there was a significant increase in the need for RRT in the HES treated individuals compared to individuals treated with other fluid therapies (RR 1.31, 95% CI 1.16 to 1.49; 19 studies, 9857 patients) and the number with author-defined kidney failure (RR 1.59, 95% CI 1.26 to 2.00; 15 studies, 1361 patients). The RR of AKI based on RIFLE-F (failure) criteria also showed an increased risk of AKI in individuals treated with HES products (RR 1.14, 95% CI 1.01 to 1.30; 15 studies, 8402 participants). The risk of meeting urine output and creatinine based RIFLE-R (risk) criteria for AKI was in contrast in favour of HES therapies (RR 0.95, 95% CI 0.91 to 0.99; 20 studies, 8769 patients). However, when RIFLE-R urine output based outcomes were excluded as per study protocol, the direction of AKI risk again favoured the other fluid type, with a non-significant RR of AKI in HES treated patients (RR 1.05, 95% CI 0.97 to 1.14; 8445 patients). A more robust effect was seen for the RIFLE-I (injury) outcome, with a RR of AKI of 1.22 (95% CI 1.08 to 1.37; 8338 patients). No differences between subgroups for the RRT and RIFLE-F based outcomes were seen between sepsis versus non-sepsis patients, high molecular weight (MW) and degree of substitution (DS) versus low MW and DS (≥ 200 kDa and > 0.4 DS versus 130 kDa and 0.4 DS) HES solutions, or high versus low dose treatments (i.e. ≥ 2 L versus < 2 L). There were differences identified between sepsis versus non-sepsis subgroups for the RIFLE-R and RIFLE-I based outcomes only, which may reflect the differing renal response to fluid resuscitation in pre-renal versus sepsis-associated AKI.

¹⁷ Mutter TC, Ruth CA, Dart AB. Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. Cochrane Database Syst Rev. 2013 Jul23; 7

- M.A.R.C.O. meta-analysis

No statistically significant difference in incidence of acute kidney injury was identified for HES products relative to comparators (crystalloid, albumin, gelatin) in this analysis.

Only three studies comparing HES and crystalloid reported any events of acute kidney injury, and the criteria used for reporting these events were different in all three studies. The low numbers of events of kidney injury observed in direct comparisons of HES with crystalloid may reflect the short length of follow up and/or small trial size. Very few events of re-operations were observed, and therefore no conclusions can be drawn regarding these endpoints.

Table 2 - Acute Kidney Injury – Combined HES (0.4 – 0.7) vs. combined comparators

| | Combined HES | Combined Comparators |
|---|---------------------|-----------------------------|
| AKI | 1.3% (16/1235) | 1.0% (13/1262) |
| Common Risk Ratio (HES over comparators) | 1.21; p=0.59 | |

Most of the additional studies submitted by the MAHs as evidence for the quantification of risk of renal injury have involved very small samples and therefore it is not possible to draw any conclusion from these data (e.g. Hokema *et al.* 2011; Fenger-EriksenC *et al.* 2005¹⁸; Akkucuk FG *et al.* 2013¹⁹ Alavi SM *et al.* 2012²⁰).

Safety data from the Rational Fluid Therapy in Germany (RaFTinG) clinical registry

The results of this study showed that the crude incidence of acute kidney injury (AKI) as judged by RIFLE-F criterion was 12.3% for all patients. Compared to crystalloid infusion only, colloids did not alter the adjusted risk of AKI significantly. In addition, the results showed that during ICU stay 7.9% of all patients received renal replacement therapy. The crude incidence of RRT was considerably higher for patients treated with colloids (13.7%) as compared with those treated with crystalloids only (3.1%). Compared with solely treatment with crystalloids only, colloids per se did not modify the adjusted risk of renal replacement therapy

In sub-group analyses, receiving HES 130/0.4 significantly reduced this risk for renal failure according to RIFLE in the subcohort of surgical patients. This effect could not be observed for medical patients.

The results presented from RaFTinG show no statistically significant differences between patients treated with crystalloids only (n=2482) and those treated with colloids (all HES preparations and gelatin, n=2063) for the endpoints AKI and RRT. For the sub-group analysis comparing crystalloid only with HES 130/0.4 a significantly lower rate of AKI is reported for HES 130/0.4 compared with crystalloids only (OR 0.582, 95 % CI 0.386 – 0.877).

Non-significant trends favouring HES 130/0.4 were reported for RRT (OR 0.980, 95 % CI 0.599 – 1.606), ICU mortality (OR 0.858, 95% CI 0. 560 – 1.315). The numbers of patients included in this

¹⁸ Fenger-Eriksen C, Hartig Rasmussen C, Kappel Jensen T, Anker-Moller E, Heslop J, Frokaer J, Tonnesen E. Renal effects of hypotensive anaesthesia in combination with acute normovolaemic haemodilution with hydroxyethyl starch 130/0.4 or isotonic saline. *Acta Anaesthesiol Scand* 2005 Aug; 49(7):969-74

¹⁹ Akkucuk FG, Kanbak M, Ayhan B, et al. The Effect of HES (130/0.4) Usage as the Priming Solution on Renal Function in Children Undergoing Cardiac Surgery. *Ren Fail.* 2013; 35(2):210-15

²⁰ Alavi SM, Ahmadi BB, Baharestani B, Babaei T. Comparison of the effects of gelatin, Ringer's solution and a modern hydroxyl ethyl starch solution after coronary artery bypass graft surgery. *Cardiovasc J Afr* 2012; 23: 428-431

subgroup analysis for crystalloids only (n=1885) and HES 130/0.4 (n=1127) differ from the numbers of patients assessed for baseline characteristics; crystalloids only (n=2482), HES 130/0.4 (n=1142). The reason for exclusion of patients, including a large number of patients from the crystalloid only group, from the subgroup analysis is not apparent.

Overall the results from RaFTinG do not show an increased risk for renal endpoints considered in patients admitted to ICU receiving colloids compared with crystalloids only, or for a subgroup of ICU patients receiving HES 130/0.4 compared with crystalloids only. As outlined previously, the observational nature of this study mean only limited conclusions can be drawn on relative benefits and risks of HES compared with crystalloids and other colloids. Furthermore, only limited data from the RaFTinG study were provided.

Spontaneous adverse drug reaction

EudraVigilance data

Data were extracted from EudraVigilance database for HES solutions for infusion.

A total of 408 case reports were retrieved, of which 31 case reports described a fatal outcome. The most frequent adverse reactions (ADR) reported were skin and subcutaneous disorders, respiratory, thoracic and mediastinal disorders, and general disorders and administration site conditions.

Because of the limitations of spontaneous ADR reports, little additional information is provided by these data on the benefit-risk balance and the renal and mortality risks of HES.

Stakeholders' submissions

The PRAC noted and assessed the stakeholders' submissions which comprised data from randomised trials, observational studies, database, retrospective cohort studies, meta-analyses and systematic review. There were 97 submissions received in total. These included 78 submissions where the benefit/risk balance of HES was claimed to be favourable in some groups of patients and the most frequent reason for that was related to the good clinical experience with the use of HES in intensive care.

Overall data provided as stakeholders' responses are consistent with the evidence that HES increases the risk of renal dysfunction in critically ill and septic patients. These are on-going randomised trial and a retrospective cohort study that do not appear to show statistically significant effects of renal injury or mortality for HES in surgical patients (e.g. Cochrane review by Mutter *et al.* 2013). No additional details on the characteristics of the database used in the retrospective cohort study are available at present. There are limitations of the data that were acknowledged. The submissions also included small studies where the use of HES in elective surgery was associated with no harm in this specific population. However, the PRAC noted that these studies were conducted in a limited number of patients.

Ad hoc expert meeting

The PRAC consulted an *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 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 early in the course of treatment of severe hypovolaemia due to bleeding i.e. in the perioperative setting and disappearing fast as the patient becomes more stable.

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.

Conclusion on safety

The PRAC reviewed all safety data of hydroxyethyl starch, with a particular focus on the risk of mortality and renal injury. These included data that from clinical studies, meta-analyses of clinical studies, post-marketing experience, responses submitted by the marketing authorisation holders (MAHs) in writing and at oral explanations and stakeholders' submissions.

On the basis of the available data, in particular results from VISEP, 6S and CHEST studies, the PRAC concluded that HES is associated with an increased risk of mortality and renal failure in patients with sepsis, in critically ill and burn patients and that the benefits of HES do not outweigh the risks in these patient populations.

The PRAC noted the available data from studies in surgical and trauma patients and considered that although these studies were limited in size and duration of follow-up they did provide some reassurance that the risks of mortality and renal injury in surgical and trauma patients may be lower than those in the critically ill and patients. Although the mechanisms by which increased renal injury and mortality occur is not well established, it is possible that the degree of inflammatory processes seen in sepsis and critically ill patients is greater and associated with significant capillary leakage compared with other patient populations such as the perioperative setting after elective surgery or uncomplicated trauma where the systematic inflammatory process and the extent of capillary leak may be lower.

The PRAC concluded that studies are needed to investigate the safety of HES in elective surgery and trauma patients.

2.1.2. Clinical efficacy

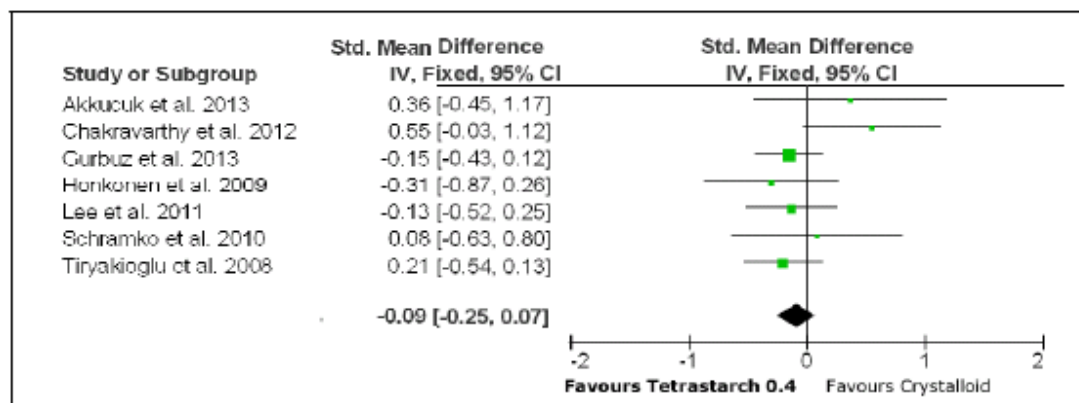
Clinical data in support of the clinical efficacy of HES solutions for infusion in surgical patients (including cardiac surgery and elective caesarean section under spinal anaesthesia), trauma patients including patients with severe haemorrhage were submitted. The data from the most relevant studies or analyses are summarised hereafter. The overview also includes data previously considered by the PRAC as part of the assessment of the referral under Article 31 of Directive 2001/83/EC.

Surgical patients

- M.A.R.C.O meta-analysis

In this meta-analysis, total blood loss referred to intraoperative blood loss and blood loss up to 24 hours after the end of the operation. The results showed the estimated difference in blood loss between HES and crystalloid from the seven trials analysed was – 0.09, in favour of HES (CI 95% - 0.25 – 0.07). This was not statistically significant, and this is not of any clinical relevance. However, in this meta-analysis HES (130/0.4) was reported to be comparable in terms of total blood loss. The results are shown in the table 3.

Table 3 - Total Blood Loss – Tetrastarch 0.4 vs crystalloid



- Martin G *et al.* 2002²¹

Martin *et al.* (2002) studied the effects of different fluids on the coagulation profile in a prospective, randomised, double-blind trial of patients undergoing major elective surgery (non cardiac surgery) with an anticipated blood loss >500 mL. The effect of lactated Ringer's solution, 6% hetastarch (HES 550) in a balanced electrolyte solution, and 6% hetastarch in normal saline on coagulation as determined by thromboelastography was compared. A total of 90 patients undergoing elective non-cardiac surgery were enrolled with 30 patients in each group, study fluids were administered intraoperatively based on a fluid administration algorithm.

Ringer's lactate-treated patients developed a hypercoagulable state until post-operative day 1, while in patients treated with HES in normal saline a hypocoagulant effect was seen post-surgery, which was reversible within 24 hours. HES in the balanced electrolyte solution did not disturb coagulation after surgery and showed some, minor degree of a hypercoagulant state at 24 h after operation. HES treatment resulted in a significantly lower estimated blood loss. There was no difference in red blood cells, or blood product utilisation among the groups. HES administration resulted in a better coagulation profile as determined by thromboelastography in comparison to lactated Ringer's solution.

- Hamaji A *et al.* 2013²²

Hamaji *et al.* (2013) reported a small randomised, controlled trial in 48 patients scheduled for hip arthroplasty with spinal anaesthesia. Patients received either a preload of 15 mL/kg HES 130/0.4 (n=24) or a preload of 30 mL/kg lactated Ringer's solution (n=24) before surgery.

²¹ Martin G, nett-Guerrero E, Wakeling H, Mythen MG, el-Moalem H, Robertson K, Kucmeroski D, Gan TJ. A prospective, randomized comparison of thromboelastographic coagulation profile in patients receiving lactated Ringer's solution, 6% hetastarch in a balanced-saline vehicle, or 6% hetastarch in saline during major surgery. *J Cardiothorac Vasc Anesth* 2002; 16: 441-446

²² Hamaji A, Hajjar L, Caiero M, Almeida J, Nakamura RE, Osawa EA, Fukushima J, Galas FR, Auler Junior JO. Volume replacement therapy during hip arthroplasty using hydroxyethyl starch (130/0.4) compared to lactated Ringer decreases allogeneic blood transfusion and postoperative infection. *Rev Bras Anesthesiol.* 2013 Jan-Feb;63(1):27-35

Significantly fewer red blood cell transfusions were required in the HES group (17% HES vs. 46% Ringer's solution). In the Ringer's solution group 11 patients (46%) needed red blood cell transfusion compared with four patients (17%) in the HES group ($p = 0.029$). Postoperative infections were less frequent in the HES group (0) compared with the Ringer's group (4/27, 17%) ($p=0.03$). There were no significant differences between groups in mortality, hospital length of stay and clinical complications other than infection.

- Moretti EW *et al.* 2003²³

Moretti *et al.* (2003) performed a prospective, blinded study in 90 patients (30 patients per group) undergoing major elective general, gynaecological, orthopaedic or urologic surgery with an anticipated blood loss of >500 mL and under maintenance of predefined haemodynamic targets. Patients were enrolled to one of 3 different resuscitation therapies requiring the administration of the following: 1301 ± 1079 mL of 6% hetastarch in saline, 1448 ± 759 mL 6% hetastarch in balanced salt, or 5946 ± 1909 mL lactated Ringer's solution. The colloid groups had significant smaller odds of nausea, nausea severity, emesis, antiemetic use, severe pain, periorbital oedema and double vision. The MAH claimed that the use of colloid led to improvement in the quality of postoperative outcome.

- Clinical trial (NCT01117649)²⁴

Details of a randomised, controlled, double-blind, multicentre phase IV clinical trial (NCT01117649) was provided by one of the MAH. The aim of the study was to investigate the efficacy of target controlled fluid therapy in patients undergoing elective surgery of the pancreatic head comparing 6% HES 130/0.42 with 10% HES 130/0.42. A third group, serving as a control for descriptive analysis only, received balanced electrolyte solution.

The study was designed with an internal pilot phase to evaluate in a blinded manner the pooled variances of the primary variables (first endpoint: intra-operatively required amount of HES and second endpoint: time until fully on oral (solid) diet (days) of the HES-groups in order to re-evaluate sample size calculation. This blinded assessment of the pooled variances after recruitment of 63 patients showed that the variances were much larger than initially assumed, leading to much higher sample sizes than initially estimated. The study was terminated due to futility in accordance with the study protocol.

Evaluation of the intra-operatively required amount of HES was performed as total amount (ml) of investigational product as well as relative to body weight (ml/kg) and relative to duration of surgery (ml/h). Furthermore, total amount of fluid (i.e. including open label treatment during on-going surgery after maximal daily dose of HES had already been administered) was analysed again in ml, ml/kg and ml/h.

No substantial differences were observed between the evaluations in the full analysis set and in the intention to treat analysis.

The three groups showed significant differences based on higher doses (ml, ml/kg bodyweight and ml/h surgery) of balanced electrolyte solution compared with 6% HES and 10% HES (table 4). Using doses in ml, the analysis showed no relevant differences between 6% HES and 10% HES. When the 6% HES and 10% HES groups were combined, the comparison with balanced electrolyte showed significantly lower doses (ml, ml/kg, ml/h) compared with HES.

²³ Moretti EW, Robertson KM, el-Moalem H, Gan TJ. Intraoperative colloid administration reduces postoperative nausea and vomiting and improves postoperative outcomes compared with crystalloid administration. *Anesth Analg* 2003; 96: 611-7, table.

²⁴ Plasma Volume Replacement (PVR) Therapy With Colloid and Crystalloid Solutions.
<http://clinicaltrials.gov/show/NCT01117649>

Table 4 - Amount of double-blind trial medication administered during surgery (Full Analysis Set)

| Dosage [mL] | Tetraspan 10% | Tetraspan 6% | Sterofundin ISO |
|--------------------|---------------|--------------|-----------------|
| Number of patients | 18 | 22 | 21 |
| minimum | 500 | 750 | 250 |
| maximum | 4000 | 4000 | 4000 |
| median | 2000.0 | 2000.0 | 2500.0 |
| mean | 2041.7 | 2215.9 | 2726.2 |
| standard dev. | 862.8 | 787.9 | 1024.4 |

The inclusion of the open label infusion after consumption of the blinded investigational product (i. e. after having administered the allowed maximal dose with respect to HES) did not alter the results as for the overall group comparison as described before for the full analysis set. In the *per* protocol set analysis the difference between the groups was less pronounced. The analysis was not altered for the combination of the two HES groups in comparison with balanced electrolyte.

For the second primary variable of time until fully on oral (solid) diet, no statistically significant group differences were detected. No statistically significant differences were observed with regard to intraoperative initial haemodynamic stabilisation. The intraoperative stroke volume (oesophageal Doppler Cardio Q, Pulse Contour Continuous Cardiac Output) and central venous pressure (CVP) were statistically significantly higher in the HES groups compared with balanced electrolyte.

- Yang J *et al.* 2011²⁵

A randomised, open-label study examined the effects of different volume replacement regimens on inflammatory response and liver function in patients with hepatocellular carcinoma undergoing hepatectomy. Patients received 20% human albumin (group 1, HA group; n=30), 6% HES 130/0.4 (group 2, HES group; n=30), or crystalloids (lactated Ringer's (LR); group 3, LR group; n=30). Additional crystalloid solutions were administered to maintain central venous pressure (CVP) between 5 and 9 mmHg throughout the period in the ICU and a mean arterial pressure (MAP) of 60–80 mmHg throughout the remainder of the study period. Total bilirubin, alanine aminotransferase, and aspartate aminotransferase increased from baseline in all groups, and did not differ significantly between groups. Morbidity including postoperative complications and mortality during the study period in the HA group and the HES group were significantly better than in the LR group (no death were reported during the study and there were no cases of renal failure in any treatment group). The length of ICU stay was similar in all groups, but the duration of postoperative hospitalisation was significantly shorter in the HA and HES groups (HA: 7.6±0.9 days, HES: 7.6±0.6 days, and LR: 8.6±1.3 days, P <0.001). C-reactive protein levels were significantly lower in the HES group (P <0.001) indicating more favourable effects on the acute phase response.

The study by Yang *et al.* (2011) suggests benefit for HES in hepatectomy.

- Other studies in cardiac surgery, elective caesarean section under spinal anaesthesia, thermal injury and neurosurgery patients

A number of other studies in the cardiac surgery setting were provided (Alavi *et al*; Gondos *et al*²⁶; Magder *et al*²⁷; Verheij *et al*²⁸; Sirvinskas *et al*; Kvalheim *et al*; Ali and Saleh; Gurbuz *et al*²⁹; Lee *et*

²⁵ Yang J, Wang WT, Yan LN, Xu MQ, Yang JY. Alternatives to albumin administration in hepatocellular carcinoma patients undergoing hepatectomy: an open, randomized clinical trial of efficacy and safety. Chinese medical journal 2011; 124: 1458-1464

²⁶ Gondos T, Marjanek Z, Ulakcsai Z, Szabo Z, Bogar L, Karolyi M, Gartner B, Kiss K, Havas A, Futo J. Short-term effectiveness of different volume replacement therapies in postoperative hypovolaemic patients. European journal of anaesthesiology 2010; 27: 794-800

al³⁰). The studies consistently show better haemodynamic outcomes, reduced time in ICU and reduced hospital stay for HES compared with crystalloid. The qualitative impression is that short term survival and renal dysfunction was similar for crystalloid and colloid in the studies presented. However the PRAC noted that long term survival data are not available and that the studies are of small size.

A number of studies from the literature in which volume preloading prior to elective caesarean section under spinal anaesthesia with either HES or crystalloid were compared for the prevention of hypotension were also submitted (French *et al.* 1999; Hasan *et al.* 2012; Madi-Jebara *et al.* 2008; Siddik *et al.* 2000; Riley *et al.* 1995; Ueyama *et al.* 1999). The studies demonstrated that there was less hypotension and a lesser requirement for sympathomimetic vasoconstrictor drugs in the groups treated with HES. The outcome for the neonate was no different regardless of whether the mother received colloid or crystalloid (as measured by APGAR score and foetal acidosis). The PRAC noted that the observation periods were short in all of the studies described and that long-term safety and mortality in mother and child were not assessed in any of the studies.

Studies in thermal injury and neurosurgery patients were submitted by the MAHs (Mokline *et al.* 2012; Vlachou *et al.* 2010; Schiller *et al.* 1997; Lindroos *et al.* 2013). The studies were limited by their small size, and by having designs not intended to provide information on long-term safety outcomes or the overall benefit-risk balance of HES.

Trauma patients

The MAHs made reference to studies which were already discussed by the PRAC in the context of the referral under Article 31 of Directive 2001/83/EC (i.e. James MF *et al.* 2011³¹, Neff TA *et al.* 2003³², Myburgh J *et al.* 2012³³, Perel P *et al.* 2011³⁴).

- Ogilvie *et al.* (2010)³⁵

Ogilvie *et al.* describes an observational study which examined death rates in trauma patients at a single centre in the USA and compared the rate for those who received standard of care with that for patients who received 6% hetastarch. The results showed that the overall mortality is significantly reduced after HES treatment compared to standard of care (5.2% vs 8.9% p= 0.0035).

The study is not a randomised trial so there is clear potential for bias and a disproportionate number of death occurred in the standard of care treatment group within 30 minutes after arrival at the trauma centre which might indicate a selection bias. The data are not sufficient robust data to allow for

²⁷ Magder S, Potter BJ, Varennes BD, Doucette S, Fergusson D; Canadian Critical Care Trials Group. Fluids after cardiac surgery: a pilot study of the use of colloids versus crystalloids. *Crit Care Med* 2010 Nov; 38(11):2117-24

²⁸ Verheij J, Van LA, Beishuizen A, Christiaans HM, de J, Girbes AR, Wisselink W, Rauwerda JA, Huybregts MA, Groeneveld AB. Cardiac Response Is Greater for Colloid Than Saline Fluid Loading After Cardiac or Vascular Surgery. *Intensive care medicine* 2006; 32: 1030-1038

²⁹ Gurbuz HA, Durukan AB, Salman N, Tavlasoglu M, Durukan E, Ucar HI, Yorgancioglu C. Hydroxyethyl starch 6%, 130/0.4 vs. a balanced crystalloid solution in cardiopulmonary bypass priming: a randomized, prospective study. *J Cardiothorac Surg* 2013; 8: 71

³⁰ Lee JS, Ahn SW, Song JW, Shim JK, Yoo KJ, Kwak YL. Effect of hydroxyethyl starch 130/0.4 on blood loss and coagulation in patients with recent exposure to dual antiplatelet therapy undergoing off-pump coronary artery bypass graft surgery. *Circ J* 2011; 75: 2397-2402

³¹ 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

³² 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

³³ Myburgh J, Finfer S, Bellomo R et al for the CHEST Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care. Published on 17 October 2012 at NEJM.org

³⁴ Perel P, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev*. 2011 Mar 16; (3):CD000567

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

conclusion on the benefits in this setting, indeed the authors conclude that a randomised blinded trial is necessary before their results can be accepted with confidence.

- Guidry *et al.* (2013)³⁶

Guidry *et al.* report a retrospective analysis in trauma patients receiving high ratios of fresh frozen plasma/packed red blood cells in damage control resuscitation (DCR). In total, 56 patients were included, 28 each in the crystalloid and colloid groups (Hextend = 6% hetastarch in an electrolyte solution). Ten-day mortality in the colloid group (7.1 %) was significantly lower in comparison to the crystalloid group (39.9 %, $p=0.004$). In addition, significantly greater volumes of crystalloid were infused.

The results of the study implied that there may be a lower risk of death in patients receiving HES compared with those receiving crystalloid. The authors concluded "A multi-institutional analysis is needed in order to validate these results."

Volume sparing effect of colloids

The MAHs claimed that the volume efficacy of iso-oncotic colloids (including HES) is higher compared to crystalloid solutions, and less colloid volume is needed to stabilise the patient haemodynamically (e.g. Jacob *et al.* 2013³⁷; Feldheiser *et al.* 2013³⁸). Furthermore, some studies showed that colloids exert lower extravascular extravasation, and improved tissue perfusion, especially in initial phase of resuscitation (e.g. Rackow *et al.* 1983³⁹, Trof *et al.* 2010⁴⁰). They also claimed that in the hypovolaemic patient with normal pulmonary function, the use of colloids to maintain colloid-osmotic pressure may limit the development of peripheral as well as pulmonary oedema (Vincent JL 2000⁴¹). It is suggested that colloids might help preventing positive fluid balance and/or over-infusion of fluids (Wills 1995, Naing CM and Win DK 2010⁴²). The MAHs also considered that a positive net fluid balance is associated with a decrease in organ perfusion and an increased mortality (e.g. Sadaka F *et al.* 2013⁴³, Payen D *et al.* 2008⁴⁴). Meybohm P *et al.* 2013⁴⁵ suggest that use of HES should be restricted to the initial phase of volume resuscitation with a maximum time interval of 24 h.

Conclusion on efficacy

The PRAC was of the opinion that short-term haemodynamic improvements have been observed in other patient populations, including surgical and trauma patients. Whilst recognising the limitations of these studies which included limited size and short-term follow-up in many studies, the PRAC noted that some volume sparing effect was reported in Madi-Jebara *et al.* 2004, that suggested that HES

³⁶ Guidry C, Gleeson E, Simms ER, Stuke L, Meade P, McSwain NE Jr, Duchesne JC. Initial assessment on the impact of crystalloids versus colloids during damage control resuscitation. *J Surg Res.* 2013 Jun 15. pii: S0022-4804(13)00568-4

³⁷ Jacob M. Chapter 10. The pharmacology of colloid solutions. pp.72-80. In: Jacob M, Nohé B. *Rational Fluid and Volume Therapy in Anaesthesia and Intensive Care Medicine.* 2013 UNI-MED Verlag AG, Bremen, International Medicinal Publishers (London, Boston)

³⁸ 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

³⁹ Rackow EC, Falk JL, Fein A, et al. Fluid resuscitation in circulatory shock: a comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. *Crit Care Med* 1983; 11(11):839-50

⁴⁰ Trof JR, Sukul SP, Twisk JWR et al. Greater cardiac response of colloid than saline fluid loading in septic and non-septic critically ill patients with clinical hypovolaemia. *Intensive Care Med* 2010; 36(4):697-701

⁴¹ Vincent JL. Issues in contemporary fluid management. *Crit Care* 2000; 4(Suppl 2):S1-2

⁴² Naing CM, Win DK. Do colloids in comparison to crystalloids for fluid resuscitation improve mortality? *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2010; 104(5):311-2

⁴³ Sadaka F, Juarez M, Naydenov S, et al. Fluid Resuscitation in Septic Shock: The Effect of Increasing Fluid Balance on Mortality. *J Intensive Care Med.* 2013 Feb 27. [Epub ahead of print]

⁴⁴ Payen D, De Pont AC, Sakr Y, et al. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. *Crit Care* 2008; 12(3):R74

⁴⁵ Meybohm P, Van Aken H, De Gasperi A, et al. Re-evaluating currently available data and suggestions for planning randomised controlled studies regarding the use of hydroxyethyl-starch in critically ill patients - a multidisciplinary statement. *Crit Care* 2013; 17:R166[Epub ahead of print]

130/0.4 6% seems to have benefits over twice the volume of Ringer's lactate in preventing spinal anaesthesia induced hypotension. Some benefit for elective surgical patients has also been shown in short-term surrogate hemodynamic outcomes along with a modest volume sparing effect (Hartog *et al.* 2011⁴⁶). In hypovolaemic patients with normal pulmonary function, the use of colloids to maintain colloid-osmotic pressure may limit the development of peripheral as well as pulmonary oedema (Vincent JL 2000). Some publications also suggest that colloids might help to prevent positive fluid balance and/or over-infusion of fluids (Wills 1995, Naing CM and Win DK 2010). Some of authors argue that a positive net fluid balance is associated with a decrease in organ perfusion and an increased mortality (e.g. Sadaka F *et al.* 2013, Payen D *et al.* 2008). Meybohm P *et al.* 2013 suggest that use of HES should be restricted to the initial phase of volume resuscitation with a maximum time interval of 24 h. Martin *et al.* 2002 showed that HES treatment resulted in a significantly lower estimated blood loss and that there was no difference in red blood cells, or blood product utilisation among the groups. Hamaji *et al.* 2013 also showed significantly fewer red blood cell transfusions were required in the HES group.

Given the lack of robust evidence to demonstrate that the short-term hemodynamic benefit shown translates into efficacy in terms of long-term patient relevant outcomes, PRAC agreed that further studies are needed to evaluate the efficacy of HES in elective surgery and trauma patients.

2.2. Risk minimisation activities, including communication

The PRAC recommended the following activities to minimise the risks.

Amendments to the product information

Based on the above assessment, the PRAC recommended amendments to the product information for hydroxyethyl starch containing products for solutions for infusion.

The amendments aim to reflect a restricted indication.

The amendments also aim to minimise the risk of mortality and renal failure associated with HES and require close monitoring of the renal function during treatment to be performed and that use of HES is contraindicated in patients with sepsis, critically patients and burns patients.

Furthermore, the PRAC decided that hydroxyethyl starch-containing products should be included in the additional monitoring list. Therefore, further amendments have been included in the product information.

More details on the proposed changes to the product information can be found in the relevant section.

Information and awareness of the Healthcare professionals and Patients

Educational measures are necessary in order to clearly inform prescribers and patients on the risk of mortality and renal failure associated with HES and on the measures necessary to minimise the risk.

Direct healthcare professional communication (DHPC)

Core elements of a direct healthcare professional communication (DHPC) were agreed during the assessment of these medicinal products to inform the healthcare professionals on the outcome of the procedure and the changes to the use of HES-containing medicinal products.

⁴⁶ 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

Future Monitoring

i. Randomised clinical trials (RCT)

As a condition to the marketing authorisations, the PRAC requested the MAHs to perform large randomised clinical trials in order to demonstrate the efficacy and safety of hydroxyethyl starch containing products in the perioperative and trauma populations. The following meaningful endpoints should be considered:

Composite primary endpoints

90-day mortality and 90-day renal failure

Secondary endpoints

- major peri-operative complications (e.g. infections, bleedings, anastomosis insufficiency, reoperation rate, diagnosis of pulmonary oedema).
- haemodynamic stabilisation in relation to dose (e.g. Heart rate, mean arterial pressure, central venous pressure, central venous oxygen saturation, serum lactate level, base excess and urine output)
- length of stay, morbidity, coagulation, inflammation, hospital mortality
- measurement of creatinine (GFR)

The synopsis of the studies should be submitted to the NCAs within 2-month of the CMDh agreement/ European Commission (EC) decision. The final protocol of the studies should be submitted to the NCAs within 6-month of the CMDh agreement/ EC decision. The results studies should be made available by end of 2016.

ii. Drug utilisation study (DUS)

As a condition to the marketing authorisations, the MAHs should conduct a drug utilisation study (DUS) (or survey) in several member states to evaluate the effectiveness of the risk minimisation measures taken. This drug utilisation study should aim to characterise prescribing practices during typical clinical use in representative groups of prescribers.

iii. Risk management plan (RMP)

The MAHs are encouraged to submit RMPs to NCAs.

2.3. Product information

Summary of product characteristics

The PRAC concluded that hydroxyethyl should be subject to additional monitoring. Therefore the following sentence is to be added into the SmPC : "**▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.**"

Section 4.1 Therapeutic indication

The wording of this section should be read as below:

Treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient. (see sections 4.2, 4.3 and 4.4)

Section 4.2 Posology and method of administration

The PRAC considered that use of HES should be restricted to the initial phase of volume resuscitation with a maximum time interval of 24.

The PRAC also recommended that the first 10-20 ml should be infused slowly and under careful monitoring of the patient so that any anaphylactoid reaction can be detected as early as possible. The section should reflect the maximum daily dose is 30ml/kg for 6% HES (130/0.40) and 6% HES (130/0.42). The maximum daily dose may be different between HES products and therefore this dose should be recalculated accordingly for other HES products.

The PRAC considered that the lowest possible effective dose should be applied. The PRAC also recommended that the treatment should be guided by continuous haemodynamic monitoring so that the infusion is stopped as soon as appropriate haemodynamic goals have been achieved. The maximum recommended daily dose must not be exceeded.

The PRAC considered that since data are limited in children, it is recommended not to use HES products in this population.

Section 4.3 Contraindications

The PRAC considered that the following contraindications should be added to this section:

- hypersensitivity to the active substances or to any of the other excipients listed in section 6.1
- sepsis
- burns
- renal impairment or renal replacement therapy
- intracranial or cerebral haemorrhage
- critically ill patients (typically admitted to the intensive care unit)
- hyperhydration
- pulmonary oedema
- dehydration
- hyperkalaemia [*only applicable to products containing potassium*]
- severe hypernatraemia or severe hyperchloraemia
- severely impaired hepatic function
- congestive heart failure
- severe coagulopathy
- organ transplant patients

Section 4.4 Special warnings and precautions for use

The PRAC recommended for warnings to be included in this section.

The section should reflect the risk of allergic (anaphylactoid) reactions, the patient should be monitored closely and the infusion instituted at a low rate.

In surgery and trauma, the PRAC considered that there is a lack of robust long term safety data in patients undergoing surgical procedures and in patients with trauma. The expected benefit of treatment should be carefully weighed against uncertainty with regard to this long term safety. Other available treatment options should be considered.

The PRAC indicated that volume replacement with HES has to be considered carefully, and haemodynamic monitoring is required for volume and dose control

The PRAC recommended that volume overload due to overdose or too rapid infusion must always be avoided. The dosage must be adjusted carefully, particularly in patients with pulmonary and cardiocirculatory problems. Serum electrolytes, fluid balance and renal function should be monitored closely.

This section was also amended to reflect that HES products are contraindicated in patients with renal impairment or renal replacement therapy and that the use of HES must be discontinued at the first sign of renal injury.

It is also reflected that an increased need for renal replacement therapy has been reported up to 90 days after HES administration and that monitoring of renal function in patients is recommended for at least 90 days.

The PRAC recommended that particular caution should be exercised when treating patients with impaired hepatic function or in patients with blood coagulation disorders. Severe haemodilution resulting from high doses of HES solutions must also be avoided in the treatment of hypovolaemic patients. In the case of repeated administration, blood coagulation parameters should be monitored carefully. The section also reflects that use of HES should be discontinued at the first sign of coagulopathy. The PRAC recommended that in patients undergoing open heart surgery in association with cardiopulmonary bypass the use of HES products is not recommended due to the risk of excess bleeding.

This section also reflects that data are limited in children therefore it is recommended not to use HES products in this population.

Section 4.8 Undesirable effects

This section was amended to include the following adverse events: hepatic injury and renal injury. It is to be noted that the frequency of these adverse events is not known (cannot be estimated from the available data).

Package Leaflet

The package leaflet was aligned to the SmPC proposals.

3. Overall discussion and benefit-risk assessment

Hydroxyethyl starch (HES) solutions for infusion include products with starch derived from potato or corn with different molecular weights and substitution ratios. HES containing solutions for infusion were indicated mainly for the treatment and prophylaxis of hypovolaemia and hypovolemic shock.

HES solutions have been the object of two reviews. The first review was initially started under the framework of Article 31 of Directive 2001/83/EC. The PRAC issued a recommendation on available data for this review in June 2013, concluding that HES solutions should be suspended in all patient populations. Following requests for re-examination by marketing authorisation holders (MAHs), the PRAC confirmed its previous position under the Article 31 in October 2013. While the re-examination was ongoing some Member States decided to suspend or limit the marketing or use of these medicines in their territories. In accordance with the EU legislation, this type of action required that an EU review procedure be carried out. Consequently, a second review of HES solutions under Article 107i of Directive 2001/83/EC was initiated, and it ran separately but in parallel with the re-examination of the Article 31, also finalising in October 2013. However, it must be noted that new evidence was considered in the procedure under Article 107i of Directive 2001/83/EC. This new evidence was not available when the PRAC recommendation on the procedure under Article 31 of Directive 2001/83/EC was issued in June 2013 and could therefore not be considered in the re-examination of the latter in October 2013. It is on the basis of the totality of the data available, including the new evidence, that the PRAC issued conclusion on the procedure provided for in Article 107i of Directive 2001/83/EC in October 2013. Therefore the conclusions on the Article 107i of Directive 2001/83/EC reflect the most complete and up-to-date evaluation of the available data relating to the HES containing medicinal products.

Details of this recommendation are presented hereafter.

Under the framework of the Article 107i of Directive 2001/83/EC, the PRAC considered recommendations on HES rendered in the referral under Article 31 of Directive 2001/83/EC and also reviewed available data including clinical studies, meta-analyses of clinical studies, post-marketing experience, responses submitted by the marketing authorisation holders (MAHs) in writing and at oral explanations, spontaneous reports on the safety and efficacy of hydroxyethyl starch containing products for solutions for infusion, as well as stakeholders' submissions in particular with regards to the risk of mortality and renal failure.

On the basis of the available data, in particular results from VISEP, 6S and CHEST studies, the PRAC concluded that HES is associated with an increased risk of mortality and renal failure in patients with sepsis, in critically ill and burn patients and that the benefits of HES do not outweigh the risks in these patient populations.

However, it was noted that short-term haemodynamic improvements have been observed in other patient populations, including surgical and trauma patients. Whilst recognising the limitations of these studies which included limited size and short duration of follow-up, the PRAC noted that some volume sparing effect was reported in Madi-Jebara *et al.* 2004, that 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. Some benefit for elective surgical patients has also been shown in short-term surrogate hemodynamic outcomes along with a modest volume sparing effect (Hartog *et al.* 2011). In hypovolaemic patients with normal pulmonary function, the use of colloids to maintain colloid-osmotic pressure may limit the development of peripheral as well as pulmonary oedema (Vincent JL 2000). Some publications also suggest that colloids might help to prevent positive fluid balance and/or over-infusion of fluids (Wills 1995, Naing CM and Win DK 2010). Some of authors argue that a positive net

fluid balance is associated with a decrease in organ perfusion and an increased mortality (e.g. Sadaka F *et al.* 2013, Payen D *et al.* 2008). Meybohm P *et al.* 2013 suggest that use of HES should be restricted to the initial phase of volume resuscitation with a maximum time interval of 24 h. Martin *et al.* 2002 showed that HES treatment resulted in a significantly lower estimated blood loss and that there was no difference in red blood cells, or blood product utilisation among the groups. Hamaji *et al.* 2013 also showed that significantly fewer red blood cell transfusions were required in the HES group.

Therefore, the PRAC noted the available data from studies in surgical and trauma patients and considered that although these studies were limited in size and duration of follow-up they did provide some reassurance that the risks of mortality and renal injury in surgical and trauma patients may be lower than those in the critically ill and patients. Although the mechanisms by which increased renal injury and mortality occur is not well established, it is possible that the degree of inflammatory processes seen in sepsis and critically ill patients is greater and associated with significant capillary leakage compared with other patient populations such as the perioperative setting after elective surgery or un-complicated trauma where the systematic inflammatory process and the extent of capillary leak may be lower.

New results from CRYSTAL have also become available. Despite the studies' limitations which were noted, the results from the CRYSTAL study comparing colloids to crystalloids showed that in patients with hypovolemia, the use of colloids vs crystalloids did not result in a significant difference in 28-day mortality. Although 90-day mortality was lower among patients receiving colloids, this requires further investigations. In addition, in the BaSES study, the hospitalisation time was significantly reduced in patients treated with 6% HES 130/0.4 compared to 0.9% NaCl. Results from the RaFTinG registry in intensive care units, an observational, non-randomised study aiming to gather more information in 'real-life' clinical practice showed no statistically significant differences between patients treated with crystalloids only (n=2482) and those treated with colloids (all HES preparations and gelatin, n=2063) for the endpoints of 90-day mortality. The PRAC therefore acknowledged the results of this studies which shows no risk of mortality associated with the use of HES but considered that given the limitations of this study its findings could not negate the findings from 6S and VISEP studies that had shown an increased risk of mortality in critically ill patients.

Additional expert advice was sought from an ad-hoc expert group. The experts agreed that the benefits may be observed 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 benefit of HES may be seen in particular in perioperative bleeding.

Therefore, the PRAC agreed that the therapeutic indication of HES containing products should be restricted to treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient. However additional measures must be implemented to minimise potential risks in these patients. HES solutions should be restricted to the initial phase of volume resuscitation with a maximum time interval of 24 h. The posology section should identify the maximum daily dose and should recommend that the lowest possible effective dose should be employed. HES products are contraindicated in patients with renal impairment or renal replacement therapy but the contraindications should also be extended to include other patient populations including patients with sepsis, critically ill patients and burns patients. The PRAC considered that the use of HES must be discontinued at the first sign of renal injury. Monitoring of renal function in patients is recommended for at least 90 days. Particular caution should be exercised when treating patients with impaired hepatic function or in patients with blood coagulation disorders. The product information will be updated to reflect these restrictions and warnings.

In addition, two phase IV randomised clinical trials with an appropriate control and clinically meaningful endpoints will need to be conducted to provide more evidence on the efficacy and safety,

including the risk of 90-day mortality and renal failure, in perioperative and trauma populations. An European drug utilisation study will also be conducted to evaluate the effectiveness of the recommended risk minimisation measures. Protocols and results of these studies will be submitted to national competent authorities according to agreed timelines. The MAHs are also encouraged to submit risk management plans to national competent authorities.

Benefit risk balance

In view of the totality of the evidence available in the procedure under Article 107i of Directive 2001/83/EC, the PRAC considered that Hydroxyethyl starch should be restricted to the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient subject to agreed restrictions, contraindications, warnings, other changes to the product information and additional risk minimisation measures.

The PRAC conclusion in the context of the referral procedure under Article 107i of Directive 2001/83/EC included additional data 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. Therefore the conclusions on the Article 107i of Directive 2001/83/EC reflect the most complete and up-to-date evaluation of the available data relating to the HES containing medicinal products.

4. Action plan and communication plan

The PRAC considered that a Direct Healthcare Professional Communication (DHPC) was needed to communicate on the measures taken for the safe use of these medicinal products. The core elements of this DHPC were agreed by the PRAC, together with the communication plan (see attachments to this report).

The MAHs should agree the translations and local specificities of the DHPC with national competent authorities. The DHPC should be sent to specialists depending on country (anaesthesiologists, specialists in intensive care medicine, specialists in infectious diseases, specialists in renal diseases, specialists in burn care, specialists in trauma care).

5. Conclusion and grounds for the recommendation

Whereas,

- The Pharmacovigilance Risk Assessment Committee (PRAC) considered the procedure under Article 107i of Directive 2001/83/EC, for hydroxyethyl starch containing products for solutions for infusion.
- The PRAC noted the conclusions of a review under Article 31 of Directive 2001/83/EC. However, for the current procedure under Article 107i of Directive 2001/83/EC the PRAC reviewed new available data, with a focus on risk of mortality and renal failure, including clinical studies, meta-analyses of clinical studies, post-marketing experience, responses submitted by the marketing authorisation holders (MAHs) in writing and at oral explanations and stakeholders' submissions.
- The PRAC considered that the use of hydroxyethyl starch is associated with an increased risk of mortality and renal replacement therapy or renal impairment in patients with sepsis, critically ill and burn patients.

- The PRAC considered, in view of the new evidence which includes data from clinical trials, further expert advice, new proposals for additional risk minimisation measures, including restrictions on use and a commitment from the MAHs to perform additional studies in patients with trauma and in elective surgery, that the benefit of hydroxyethyl starch containing products outweighs the risk in the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient. This is subject to restrictions, warnings and other changes to the product information.
- The PRAC concluded that hydroxyethyl starch containing products should be contraindicated in patients with sepsis, in critically ill and burn patients. In addition, special warnings in surgery and trauma patients have been included.
- The PRAC also concluded that there was need for further risk minimisation measures such as information to patients and healthcare professionals. Core elements of a direct healthcare professional communication were agreed, together with the timelines for distribution, and that studies should be conducted. The PRAC also considered that studies should be conducted to provide more evidence on the efficacy and safety of hydroxyethyl starch in the perioperative setting and trauma.

The PRAC concluded that the benefit-risk balance for hydroxyethyl starch containing medicinal products remains favourable in treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient subject to the agreed restrictions, contraindications, warnings, other changes to the product information and additional risk minimisation measures.

The PRAC conclusion in the context of the referral procedure under Article 107i of Directive 2001/83/EC included additional data 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. Therefore the conclusions on the Article 107i reflect the most complete and up-to-date evaluation of the available data relating to HES containing medicinal products.

Appendix 1

Listing of submissions of all data received by the Agency

Listing of submissions of data received by the Agency (i.e. from MAHs and other stakeholders) for hydroxyethyl starch containing medicinal products

| Submission |
|---|
| MAHs |
| Serumwerk Bernburg AG |
| B.Braun Melsungen AG |
| Fresenius Kabi |
| Baxter |
| Stakeholders |
| Healthcare professional – Anaesthesiology, Greece |
| Healthcare professional - Anaesthesiology and Intensive Care Finland |
| Healthcare professional – Anaesthesia, India |
| Healthcare professional - Intensive care, India |
| Research – Department of Outcomes Research, Anaesthesiology Institute, USA |
| Healthcare professional - Intensive Care, Denmark |
| Healthcare professional –Department Anaesthesiology and Critical Care and Department of Anaesthesia, South Africa |
| Healthcare professional - Department of Anaesthesia, Philippines |
| Healthcare professional - Critical Care, India |
| Healthcare professional -Cardiac Anaesthesiology, India |
| Healthcare professional - Critical Care, India |
| Healthcare professional – Internist-intensivist, Greece |
| Healthcare professional -French Society of Anaesthesia and Intensive Care Medicine (SFAR) |
| Healthcare professional –Anaesthetist, India |
| Patient - Mexico |
| Healthcare professional - Spain |
| Healthcare professional - Anaesthesiology, Malaysia |
| Healthcare professional –Specialist anaesthetist and researcher, South Africa |
| Healthcare professional - Internist and Intensivist; Clinical Pharmacologist and Metaanalyst, Italy |
| Healthcare professional- Internist and Intensivist; Clinical Pharmacologist and Metaanalyst, Italy |

| Submission |
|---|
| Healthcare professional – Internist and Intensivist; Clinical Pharmacologist and Metaanalyst, Italy |
| Healthcare professional - Department of Anaesthesiology and Intensive Care, Center for Sepsis Control and Care, Germany |
| Healthcare professional - Transfusions, Spain |
| Healthcare professional - Anaesthesiologists, Germany |
| Healthcare professional –Critical Care Medicine, India |
| Industry – Germany |
| Healthcare professional – Intensivist, Greece |
| Healthcare professional –Emergency Dept., India |
| Healthcare professional –Department of Anaesthesiology, South Africa |
| Healthcare professional –Anaesthesiologist, Mexico |
| Healthcare professional –Mexico |
| Healthcare professional – Intensive Care specialist , Internal medicine/nephrology, Belgium |
| Healthcare professional –Intensive Care specialist, Belgium |
| Healthcare professional - Sepsis and multiple organ failure, Anaesthesiology, Germany |
| Healthcare professional - Medical specialist in Cardiovascular Anaesthesia, Mexico |
| Healthcare professional - Anaesthesiology and ICU, Argentina |
| Healthcare professional – Anesthesiologist, USA |
| Healthcare professional - German Society of Anaesthesiology and Intensive Care Medicine (DGAI), Germany |
| Healthcare professional - G.I.C.R. (gruppo interdisciplinare chimica dei radiofarmaci), Italy |
| Healthcare professional - Anaesthesiologist, France |
| Healthcare professional –Anaesthesia and Surgical ICU Department, Egypt |
| Healthcare professional - Anaesthesiology and intensive care medicine, Germany |
| Healthcare professional –Anaesthesia, India |
| Healthcare professional - Emergency medicine and critical care, México |
| Healthcare professional – Anaesthesiology, Japan |
| Healthcare professional –Anaesthesiologist and Intensivist, The Netherlands |
| Healthcare professional - Intensive Care, Belgium |
| Healthcare professional –Anaesthesiologist and Critical Care, Critical Care and Pain, India |
| Academia/student - Critical Care & Trauma Division, Australia |
| Healthcare professional - Anaesthesiology, Argentina |

| Submission |
|--|
| Healthcare professional - . Anaesthesiology and Intensive Care Medicine, Czech Republic |
| Research institute - Department of Surgery, Greece |
| Healthcare professional – Perfusionist, USA |
| Healthcare professional - Austrian Society of Anaesthesiology, Resuscitation and Intensive Care, Austria |
| Healthcare professional –Anaesthesia and Intensive Care in Cardiac Surgery, Italy |
| Healthcare professional –Anaesthesiologist, The Netherlands |
| Healthcare professional - Cardiothoracic and Vascular Anaesthesiologist, Mexico |
| Healthcare professional - Critical Care, Spain |
| Healthcare professional –Anaesthetist and researcher, Department of Anaesthesia , South Africa |
| Healthcare professional - Asian heart institute, India |
| Healthcare professional - Critical Care Medicine |
| Healthcare professional - Cardiac anaesthesiologist , USA |
| Healthcare professional - Anaesthesia and Intensive Care, France |
| Healthcare professional –Intensivist, India |
| Healthcare professional – Anaesthesia, India |
| Healthcare professional – India |
| Healthcare professional - Cardiac Anaesthesiologist and intensivist, India |
| Healthcare professional – Respiratory Medicine, Critical Care and Sleep Medicine, India |
| Healthcare professional –Intensivist,Critical Care & Emergency Medicine , India |
| Healthcare professional - Anaesthesiology and Perioperative Care, USA |
| Healthcare professional – Anaesthesia, India |
| Healthcare professional – Anaesthesiologists, Mexico |
| Healthcare professional - Anaesthesia and Intensive Care, Italy |
| Healthcare professional –Institute of Physiology and Pathophysiology, Germany |
| Healthcare professional - Education Research Foundation, India |
| Healthcare professional –Intensivist, India |
| Healthcare professional –Consultant Anaesthetist, Singapore |
| Healthcare professional –Anaesthesia, India |
| Healthcare professional –Consultant anaesthesiologist, India |
| Healthcare professional |

| Submission |
|--|
| Healthcare professional - Anaesthesiology, Spain |
| Healthcare professional - consultant anaesthetist, India |
| Healthcare professional - Paediatric Surgeon, India |
| Healthcare professional - Indian Society of Critical Care Medicine, India |
| Healthcare professional - Consultant in critical care, India |
| Healthcare professional - Anaesthesiologist , Korea Republic |
| Healthcare professional - Cardiac anaesthesiologist, India. |
| Healthcare professional - Anaesthesiology and Reanimation., Turkey |
| Healthcare professional –Anaesthesiologist, Belgium |
| Healthcare professional - Intensivist, India |
| Healthcare professional - Anaesthesiologist, India |
| Healthcare professional - Critical care, Mexico |
| Healthcare professional - Liver Transplant, Anaesthesia and Intensive Care, India |
| Healthcare professional -, National Cancer Institute, Anaesthesiology , Egypt, |
| Healthcare professional –Anaesthesia and Critical Care, India |
| Healthcare professional - India |
| Healthcare professional - Department of Anaesthesiology and Intensive Therapy, Hungary |
| Research Institute - Queen Marys University of London |

Appendix 2

Divergent positions to PRAC recommendation

Article 107i of Directive 2001/83/EC

Procedure No: EMEA/H/A-107i/1376

Solutions for infusion containing hydroxyethyl starch

Divergent statement

The following members of PRAC did not agree with the PRAC's Recommendation on the Article 107i referral resulting from pharmacovigilance data for solutions for infusion containing hydroxyethyl starch (HES) based on the following reasons:

1. Harm from use of HES compared with crystalloids in terms of increased mortality and increased renal injury, as well as other serious adverse reactions, has been shown in large well-designed randomised controlled trials in septic and critically ill patients. The available studies in elective surgery and trauma cannot provide reassurance of a lower risk than in septic and critically ill patients, or indeed exclude such a risk. The ad hoc Expert Advice Group held in September 2013 agreed that the evidence to demonstrate a lower risk of renal injury and mortality in any settings other than sepsis and the critically ill is weak.
2. There is very limited evidence on the benefits and risks of hydroxethyl starch solutions for use in elective surgery and trauma. The magnitude of the volume sparing effect of HES relative to crystalloid solutions has often been cited as 3-4 fold, however there is some evidence that this ratio is lower in surgical settings, around 1.8 fold in some types of surgery (Hartog 2011). It is unclear how the surrogate endpoints from these studies translate to clinically relevant endpoints. Both ad hoc Expert Advice Groups (meetings 19 April 2013 and 13 September 2013) commented that the data evaluating benefit in the perioperative setting and trauma setting do not adequately support a clinically relevant beneficial effect for HES.
3. There is an overlap between those patient groups where the benefit-risk balance of HES is judged to be negative (septic and critically ill patients), and the patients who will receive HES under the revised indication allowing use in patients with hypovolaemia due to acute bleeding (e.g. including the trauma and perioperative settings). In traumatic injury the patients most likely to receive HES are also those likely to have the most severe injury, and therefore have a greater degree of systemic inflammatory processes and increased risk from exposure to HES. It should also be noted that elective surgery and trauma patients can develop sepsis or complications requiring critical care and these patients cannot be identified in advance. Approximately 20% of the critically ill patients in the CHEST study entered the ICU following elective surgery (Myburgh et al, 2012).
4. The mechanism underlying the risks of renal injury and mortality observed with HES is not well understood, and therefore these should be considered to be potential risks in all patient groups. Systemic inflammatory processes may contribute to the observed increased risk in sepsis and burn injury. There is a continuum in the extent of systemic inflammation between healthy individuals and patients with sepsis or burn injury. Trauma and surgery patients are located on an intermediate position on this continuum. There is also evidence that tissue deposition of hydroxyethyl starch occurs in healthy patients without inflammatory processes (Sirtl et al, 1999).
5. Alternative treatments are available in the form of crystalloids, and high quality care is possible without the use of HES: a survey of 391 ICUs worldwide conducted in 2010 (Finfer et al, 2010) showed no use of HES in the United States or Australia.
6. Without evidence to provide reassurance that patients will not be exposed to increased risk of mortality and renal injury by use of HES, and given the lack of data supporting a clinically relevant benefit, suspension of marketing authorisations for HES products in all patient populations remains appropriate to protect public health. This would avoid the situation where patients are unnecessarily exposed to risk from treatment with HES with no convincing evidence that they are receiving any additional benefit.
7. The ability of the proposed risk minimisation measures to sufficiently minimise the risks of HES is a concern. Data are lacking to identify an appropriate maximum dose, and expert advice is that there is no absolute 'safe' lower dose below which there is no risk associated with HES

administration. The recommendation to monitor renal function in patients for at least 90 days may not be an effective measure to minimize the risk of renal injury in all patients as detection of worsening of renal function by monitoring may not be practical in patients who are discharged shortly after receiving HES. Furthermore, in emergency settings, it may be particularly difficult to evaluate patients for contraindications.

Due to the above mentioned arguments the below mentioned PRAC delegate considers the benefit-risk balance of hydroxyethyl starch (HES) to be negative in all patient populations, justifying the suspension of the marketing authorisations of all HES-containing medicinal products.

PRAC members expressing a divergent position:

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| Kamila Czajkowska (PL) | 10 October 2013 | Signature: |
| Marie Louise De Bruin | 10 October 2013 | Signature: |
| Jacqueline Genoux-Hames (LU) | 10 October 2013 | Signature: |
| Martin Huber (DE) | 10 October 2013 | Signature: |
| Brigitte Keller-Stanislawski | 10 October 2013 | Signature: |
| Maria Popova-Kiradjieva (BG) | 10 October 2013 | Signature: |
| Carmela Macchiarulo (IT) | 10 October 2013 | Signature: |
| Almath Spooner (IE) | 10 October 2013 | Signature: |
| Doris Stenver (DK) | 10 October 2013 | Signature: |
| Amy Tanti (MT) | 10 October 2013 | Signature: |
| Kirsti Villikka (FI) | 10 October 2013 | Signature: |
| Julie Williams (UK) | 10 October 2013 | Signature: |

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| Stephen Evans | 10 October 2013 | Signature: |
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Article 107i of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMA/H/A-107i/1376

Solutions for infusion containing hydroxyethyl starch (HES)

Divergent statement

The following member of PRAC did not agree with the PRAC's Recommendation on the Article 107i 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.

Harm from use of HES compared with crystalloids in terms of increased mortality and increased renal injury, as well as other serious adverse reactions, has been shown in large well-designed randomised controlled trials in septic and critically ill patients. The available studies in trauma cannot provide reassurance of a lower risk than in septic and critically ill patients, or indeed exclude such a risk. The ad hoc Expert Advice Group held in September 2013 agreed that the evidence to demonstrate a lower risk of renal injury and mortality in any settings other than sepsis and the critically ill is weak. Overall the group agreed the benefits may exist in severe hypovolaemia in short duration only at the beginning i.e. peri-operative setting and disappearing faster with patient's stabilisation.

The benefit-risk may therefore be considered favourable only in this specific population (elective surgery) 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) to be negative in populations other than elective surgery, justifying the suspension of the marketing authorisations of all HES-containing medicinal products for these indications.

PRAC members expressing a divergent position:

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|--------------------|-----------------|------------------|
| Sabine Straus (NL) | 10-October 2013 | Signature: |
|--------------------|-----------------|------------------|

Article 107i of Directive 2001/83/EC

Procedure No: EMEA/H/A-107i/1376

Solutions for infusion containing hydroxyethyl starch

Divergent statement

The following members of PRAC did not agree with the PRAC's Recommendation on the Article 107i referral resulting from pharmacovigilance data for solutions for infusion containing hydroxyethyl starch (HES) based on the following reasons:

1. Harm from use of HES compared with crystalloids in terms of increased mortality and increased renal injury, as well as other serious adverse reactions, has been shown in large well-designed randomised controlled trials in septic and critically ill patients. The available studies in elective surgery and trauma cannot provide reassurance of a lower risk than in septic and critically ill patients, or indeed exclude such a risk. The ad hoc Expert Advice Group held in September 2013 agreed that the evidence to demonstrate a lower risk of renal injury and mortality in any settings other than sepsis and the critically ill is weak.
2. There is very limited evidence on the benefits and risks of hydroxethyl starch solutions for use in elective surgery and trauma. The magnitude of the volume sparing effect of HES relative to crystalloid solutions has often been cited as 3-4 fold, however there is some evidence that this ratio is lower in surgical settings, around 1.8 fold in some types of surgery (Hartog 2011). It is unclear how the surrogate endpoints from these studies translate to clinically relevant endpoints. Both ad hoc Expert Advice Groups (meetings 19 April 2013 and 13 September 2013) commented that the data evaluating benefit in the perioperative setting and trauma setting do not adequately support a clinically relevant beneficial effect for HES.
3. There is an overlap between those patient groups where the benefit-risk balance of HES is judged to be negative (septic and critically ill patients), and the patients who will receive HES under the revised indication allowing use in patients with hypovolaemia due to acute bleeding (e.g. including the trauma and perioperative settings). In traumatic injury the patients most likely to receive HES are also those likely to have the most severe injury, and therefore have a greater degree of systemic inflammatory processes and increased risk from exposure to HES. It should also be noted that elective surgery and trauma patients can develop sepsis or complications requiring critical care and these patients cannot be identified in advance. Approximately 20% of the critically ill patients in the CHEST study entered the ICU following elective surgery (Myburgh et al, 2012).
4. The mechanism underlying the risks of renal injury and mortality observed with HES is not well understood, and therefore these should be considered to be potential risks in all patient groups. Systemic inflammatory processes may contribute to the observed increased risk in sepsis and burn injury. There is a continuum in the extent of systemic inflammation between healthy individuals and patients with sepsis or burn injury. Trauma and surgery patients are located on an intermediate position on this continuum. There is also evidence that tissue deposition of hydroxyethyl starch occurs in healthy patients without inflammatory processes (Sirtl et al, 1999).
5. Alternative treatments are available in the form of crystalloids, and high quality care is possible without the use of HES: a survey of 391 ICUs worldwide conducted in 2010 (Finfer et al, 2010) showed no use of HES in the United States or Australia.
6. Without evidence to provide reassurance that patients will not be exposed to increased risk of mortality and renal injury by use of HES, and given the lack of data supporting a clinically relevant benefit, suspension of marketing authorisations for HES products in all patient populations remains appropriate to protect public health. This would avoid the situation where patients are unnecessarily exposed to risk from treatment with HES with no convincing evidence that they are receiving any additional benefit.
7. The ability of the proposed risk minimisation measures to sufficiently minimise the risks of HES is a concern. Data are lacking to identify an appropriate maximum dose, and expert advice is that there is no absolute 'safe' lower dose below which there is no risk associated with HES

administration. The recommendation to monitor renal function in patients for at least 90 days may not be an effective measure to minimize the risk of renal injury in all patients as detection of worsening of renal function by monitoring may not be practical in patients who are discharged shortly after receiving HES. Furthermore, in emergency settings, it may be particularly difficult to evaluate patients for contraindications.

Due to the above mentioned arguments the below mentioned PRAC delegate considers the benefit-risk balance of hydroxyethyl starch (HES) to be negative in all patient populations, justifying the suspension of the marketing authorisations of all HES-containing medicinal products.

PRAC member expressing a divergent position:

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|--------------------------|-----------------|------------------|
| Ingebjørg Buajordet (NO) | 10 October 2013 | Signature: |
|--------------------------|-----------------|------------------|