Article 107i of Directive 2001/83/EC

Procedure No: EMEA/H/A-107i/1376 for solutions for infusion containing hydroxyethyl starch

The following CMDh Members support the divergent position appended to the PRAC recommendation on HES containing medicinal products dated 10 October 2013, as stated below:

CMDh members expressing a divergent position

Keith McDonald (UK)	23 October 2013	Signature: ……...
Susanne Winterscheid (BG)	23 October 2013	Signature: ……...
Jayne Crowe (IE)	23 October 2013	Signature: ……...
Jacqueline Genoux-Hames (LU)	23 October 2013	Signature: ……...
Christa Wirthumer-Hoche (AT)	23 October 2013	Signature: ……...
Sandra Petraglia (IT)	23 October 2013	Signature: ……...
Susanne Winterscheid (DE)	23 October 2013	Signature: ……...
Tuomo Lapveteläinen (FI)	23 October 2013	Signature: ……...

Divergent statement from PRAC members

Some members of PRAC did not agree with the PRAC's Recommendation on the Article 107i referral 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.

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CMDh member expressing a divergent position

Inger Heggebø (NO)	23 October 2013	Signature: ……...

<u>Divergent statement from PRAC members</u>

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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.

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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.