MHRA
Regulating Medicines and Medical Devices

NOTIFICATION OF A REFERRAL UNDER ARTICLE 107i OF DIRECTIVE 2001/83/EC
FAX NUMBER –44 20 75237051

This notification is an official referral under Article 107i of Directive 2001/83/EU made by the United Kingdom

Product Name(s), if appropriate, Strength(s) and Pharmaceutical Forms	Venofundin 6% (PL 03551/0097; B Braun Melsungen AG), Tetraspan 6% (PL 03551/0106; B Braun Melsungen AG) Tetraspan 10% (PL 03551/0107; B Braun Melsungen AG); Hyperhaes (PL 08828/0157; Fresenius Kabi Limited), Volulyte 6% (PL 08828/0174; Fresenius Kabi Limited), Voluven 6% (PL 08828/0145; Fresenius Kabi Limited) Voluven 10% (PL 08828/0207; Fresenius Kabi Limited); Plasma Volume Redibag 6% (PL 00116/0635; Baxter Healthcare Limited)
Active Substance	Hydroxyethyl starch
Marketing Authorisation Holder(s)	B Braun Melsungen AG Fresenius Kabi Limited Baxter Healthcare Limited

Hydroxyethyl starch (HES) solutions for infusion are authorised for the treatment and prophylaxis of hypovolaemia and hypovolaemic shock. On 20 November 2012, Germany informed the European Medicines Agency, pursuant to Article 31 of Directive 2001/83/EC, of their consideration to review the benefit risk balance of HES for solutions for infusion resulting from the evaluation of data relating to pharmacovigilance showing an increased risk of mortality and renal replacement therapy in patients treated with HES. On 14 June 2013, the Pharmacovigilance Risk Assessment Committee (PRAC) concluded that the benefit risk balance of hydroxyethyl starch solutions for infusion was not favourable in the approved indications in any patient population and recommended that marketing authorisations for HES products be suspended. Due to a request for re-examination of the PRAC recommendation, the Article 31 procedure is not expected to be completed until September or October 2013.

The main evidence of risk with HES comes from several published studies. Large randomised clinical trials have reported an increased risk of renal dysfunction and mortality over a 90-day follow-up in patients who received HES compared with crystalloids. Increased risk of renal dysfunction has been shown in trials of patients with sepsis[1,2] and in a large trial of critically ill patients, including a subgroup with sepsis.[3] Increased mortality at 90 days was also shown in the trials of patients with sepsis.[1,2]

The most accurate estimate of the magnitude of these risks is from meta-analyses of published data. A meta-analysis reported an increased relative risk of renal failure of 1·27 (95%CI 1·09–1·47) for HES compared with crystalloid.[4] A Cochrane review that included 25 studies with mortality data reported an

increased relative mortality risk of 1·10 (95%CI 1·02–1·19) for HES compared with crystalloid.[5]

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

There is significant concern among the UK clinical community about the safety of HES. The UK Faculty of Intensive Care Medicine and Royal College of Anaesthetists issued advice on the 16 June 2013 about the use of alternative products to HES.

On 21 June 2013, the UK Commission on Human Medicines, on review of the available data, has advised that HES products should be suspended on the following grounds.

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

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

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

In the UK there have been 45 reports of suspected adverse reactions to HES products, 3 of which were fatal. These include 3 reports of renal disorders, one of which was fatal.

Given the evidence for harm associated with HES products and the continued significant use of these products, the UK considers that there is an urgent need for national action pending the outcome of the Article 31 referral. On the basis of the advice from the Commission on Human Medicines, the UK is considering suspending the marketing authorisations for HES products in the UK.

As a result of the evaluation of data resulting from pharmacovigilance activities, the UK is referring HES solutions to the Pharmacovigilance Risk Assessment Committee and requests that it gives its urgent recommendation under Article 107i of Directive 2001/83 EEC, as amended, on whether the Marketing Authorisations for solutions for infusion containing HES medicines should be maintained, varied, suspended or withdrawn.

Signed [redacted] Date: 27 June 2013