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12th November 2013

Restriction of use of HES
(hydroxyethyl starch containing medicinal products)

HyperHAES PA0566/027/001
Voluven 6% Solution for Infusion (Glass bottle) PA566/020/001
Voluven 6% Solution for Infusion (Polyolefine/Freeflex bag) PA566/020/002
Voluven 6% Solution for Infusion (PVC bag) PA566/020/003
Voluven 10% Solution for Infusion (Polyolefine/Freeflex bag) PA566/020/004
Voluven 10% Solution for Infusion (PE bottle) PA566/020/005
Volulyte 6% Solution for Infusion (Polyolefine/Freeflex bag) PA566/037/001
Volulyte 6% Solution for Infusion (Glass bottle) PA566/037/002

Dear Healthcare Professional,

This letter is to inform you of the outcome of a recently performed evaluation of the benefits and risks of hydroxyethyl starch (HES) containing products.

The letter is being sent in agreement with the EMA (European Medicines Agency) and the Irish Medicines Board.

Summary of the new recommendations

- **HES products should only be used for the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient**

- **HES products should be used at the lowest effective dose for the shortest period of time.** Treatment should be guided by continuous haemodynamic monitoring so that the infusion is stopped as soon as appropriate haemodynamic goals have been achieved

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- **(HES) products are now contraindicated in**

  - **Sepsis**
  - **Burns**
  - **Renal impairment or renal replacement therapy**
  - **Intracranial or cerebral haemorrhage**
  - **Critically ill patients (typically admitted to the ICU)**
  - **Hyperhydrated patients, including patients with pulmonary oedema**
  - **Dehydrated patients**
  - **Severe coagulopathy**
  - **Severely impaired hepatic function**

- **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 the uncertainties with regard to long term safety and other available treatment options should be considered.**

- **Large randomised clinical trials have reported an increased risk of renal dysfunction in the critically ill, including patients with sepsis. Therefore HES should no longer be used in these patients.**

- **Monitoring of renal function in patients receiving HES is recommended and HES must be discontinued at the first sign of renal injury.**

Further information on the safety concern:

Infusion solutions containing HES belong to the class of colloids. In the EU, HES-containing solutions for infusion are approved via national procedures.

Recently, the results of two clinical trials in critically ill patients, mainly with sepsis, have been published (1,2) compared with crystalloids. The studies showed a greater risk of adverse renal effects in patients treated with HES. The study of patients with sepsis (1) also showed a greater risk of mortality in patients treated with HES.

Based on the results of these randomised controlled trials, the European Medicines Agency (EMA) in November 2012, initiated a safety review of all HES-containing products on the EU market.

The review included data from the scientific literature, data submitted by the companies, data from the authors of the studies and from the stakeholders.

In June 2013, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) recommended that the benefits of HES solutions no longer outweigh their risks and that HES containing products should be suspended from the market in the EU. Since then, the PRAC has analysed

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and considered new evidence that was not available at the time of the initial recommendation, including new studies and new proposals for additional risk minimisation measures. The companies have also committed to conduct additional studies to examine efficacy and long-term safety.

On the basis of the data available to date, the PRAC has now concluded that HES products should only be used in a restricted patient population. New contraindications and warnings are being introduced and the marketing authorisation holders are required to perform further studies. The product information will be updated with the new information.

Call for reporting

Healthcare professionals should report any suspected adverse reactions associated with use of hydroxyethyl starch in accordance with the national requirements via the national spontaneous reporting system. Please report any suspected adverse reactions to the IMB using the online system at www.imb.ie or using the yellow card system. The IMB can also be contacted on 01-6764971.

Company contact point

For further information, please contact Fresenius Kabi Ltd on ++44 (0)1928 533612 or email pharmacovigilance.GB@fresenius-kabi.com. Alternatively, contact can be made by post at the following address:

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Yours sincerely,

Fresenius Kabi Ltd

Mr Chris Harrison
Group Managing Director

Mr Tony Rigden
Head of Regulatory Affairs

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Literature:

1. Perner, A. *et al.* Hydroxyethyl Starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 2012; 367(2):124-134.
2. Myburgh, J.A. *et al.* Hydroxyethyl starch or saline for fluid resuscitation in intensive care; N Engl J Med 2012; 367(20):1901-11.