2nd July 2013

IRISH MEDICINES BOARD

European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) recommends suspension of the marketing authorisations of Infusion Solutions containing Hydroxyethyl Starch (HES)[1]

IMB Opinion on the PRAC Recommendation

Dear Healthcare Professional,

This letter is to inform you that the PRAC, where the IMB is represented, has conducted an assessment (Article 31 of Directive 2001/83/EC) of **solutions for infusion containing hydroxyethyl starch (HES)** and concluded that the benefit risk balance of these products is not favourable in the approved indications and in any patient population.

Therefore, the PRAC has recommended the suspension of the marketing authorisations for infusion solutions containing hydroxyethyl starch (HES)[1].

The PRAC recommendation is not the final step in the regulatory process. Some of the Marketing Authorisation Holders (MAHs) for HES-containing products have requested a re-examination by the PRAC and the finalised regulatory position is not anticipated until the autumn.

As a result of the prolonged regulatory process, and the emerging information from the EMA and other EU Member States, the IMB wishes to communicate that the IMB agrees with the PRAC recommendation. Pending the outcome of the re-examination procedure, the IMB would not recommend the use of these products.

Summary:

- **Following a safety review of hydroxyethyl starch (HES) containing medicinal products at European level, the PRAC has recommended that the marketing authorisations for these products be suspended.**
- **Results from large randomised clinical trials have reported an increased risk of renal dysfunction and mortality in critically ill or septic patients who received hydroxyethyl starch (HES) compared with crystalloids.**
- **MAHs have requested a re-examination of the PRAC recommendation and, therefore, the final regulatory decision is not anticipated until the autumn.**
- **Pending the outcome of the re-examination, the IMB would not recommend that HES infusion solutions be administered to patients.**

[1]. See enclosed Annex for a list of HES containing products authorised in Ireland including Brand Names and PA numbers.

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Further information:

HES-containing products are colloid solutions mainly used for fluid resuscitation in patients with hypovolaemia. Recently the results of three large clinical trials in critically ill patients, and in particular patients with severe sepsis, have been published. The studies in patients with severe sepsis demonstrate a consistent pattern of harm in terms of increased mortality and adverse renal effects[1,2]. A large study targeting a broader critically ill population indicates similar effects with no benefit, but with harm in terms of renal adverse effects[3]. Based on the results of these large randomised controlled trials the EMA initiated a safety review by the PRAC of all HES-containing products on the EU market.

The review included data from the scientific literature and the data submitted by the companies. The PRAC was of the opinion that, when compared with those given crystalloid solutions, patients treated with HES had an increased risk of acute renal injury and death. The PRAC also considered that the available data only showed limited benefit of HES in hypovolaemia, which did not justify its use considering the known risks.

The PRAC therefore recommended that the marketing authorisations for these medicines be suspended and that the suspension should remain in place unless the Marketing Authorisation Holder can provide convincing data to identify a group of patients in whom the benefits of the medicines outweigh their risks.

In line with their legal rights, some of the MAHs involved have requested a re-examination of the PRAC recommendation. This will take some time to complete and the final regulatory decision is not anticipated until the autumn.

The IMB continues its regulatory oversight by monitoring developments at European and national level. Healthcare Professionals will receive further communication as matters progress regarding further regulatory action.
For further information, please refer to the IMB (www.imb.ie) and EMA websites (www.ema.europa.eu) or contact vigilance_assessment@imb.ie.
Please report any suspected adverse reactions to the IMB using the online system at www.imb.ie or using the yellow card system.

Yours sincerely,

Joan Gilvarry

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Director of Human Medicines

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[1] *Brunkhorst, F. M., C. Engel, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008; 358(2): 125-39.*
[2] *Perner, A., N. Haase, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 2012; 367(2): 124-34.*
[3] *Myburgh, J. A., S. Finfer, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 2012;367(20): 1901-11.*

Annex

List of HES-containing products authorised in Ireland

EquiHes 60 mg/ml solution for infusion, Ecoflac Plus PA0736/024/001

EquiHes 100 mg/ml solution for infusion, Ecoflac Plus PA0736/024/002

EquiHes 60 mg/ml solution for infusion, Ecobag PA0736/024/003

EquiHes 100 mg/ml solution for infusion, Ecobag PA0736/024/004

HyperHAES solution for infusion PA0566/027/001

Voluven 6% Solution for Infusion (Glass bottle) PA0566/020/001

Voluven 6% Solution for Infusion (Polyolefine/Freeflex Bag) PA0566/020/002

Voluven 6% Solution for Infusion (PVC Bag) PA0566/020/003

Voluven 10% Solution for Infusion (Polyolefine Bag) PA0566/020/004

Voluven 10% Solution for Infusion (PE Bottle) PA0566/020/005

Volulyte 6% Solution for Infusion, polyoelfine bags PA0566/037/001

Volulyte 6% Solution for Infusion, glass bottle PA0566/037/002

*Plasma Volume Redibag 6 % Solution for Infusion PA0167/133/001

*Plasma Volume Redibag 6% Solution for Infusion, PA0167/133/001 is not currently supplied to the Irish market.