29 November 2012
EMA/PRAC/750422/2012

PRAC List of questions

To be addressed by the marketing authorisation holder(s) for solutions for infusion containing hydroxyethyl starch

Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure number: EMEA/H/A-31/1348

INN/active substance: hydroxyethyl starch

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The marketing authorisation holders MAH(s) for hydroxyethyl starch (HES) containing medicinal products, solution for infusion, are requested to provide the following:

Question No. 1

Concerning your HES containing medicinal product(s) solution for infusion, available on the EU market, please provide:

a) information on approved indication(s), concentration / molecular weight / degree of substitution of HES, doses, treatment duration, composition, contraindications, warnings and precautions, included in your summary of product characteristics (SPC). Please tabulate the main differences between the SPCs in the different countries in the EU;

b) information on marketing and legal status in different EU Member States/EEA.

Question No. 2

Please provide figures on patient exposure by product and by country for the past 5 years.

Question No. 3

In the light of new safety concerns for HES containing medicinal products, solution for infusion for the treatment of hypovolaemia and hypovolaemic shock – deriving from recently published studies – please provide a justification and relevant supporting data/evidence for the maintenance of the approved therapeutic indication(s) for patients with sepsis, including a revised SPC wording.

Please provide the above for hypertonic and isotonic HES containing medicinal products separately. Different HES formulations (130/0.4 vs. 200/0.5) should be considered as well.

Please consider (and discuss) in your response other available treatment options, i.e. other colloid solutions and crystalloid solutions.

Question No. 4

In the light of new safety concerns for HES containing medicinal products, solution for infusion for the treatment of hypovolaemia and hypovolaemic shock – deriving from recently published studies – please provide a justification and relevant supporting data/evidence for the maintenance of the approved therapeutic indication(s) in critically ill patients/ICU patients, including a revised SPC wording.

Please provide the above for the different subtypes of “hypovolaemia and hypovolaemic shock” (e.g. trauma, types of surgery, burns) together with a justification for the most appropriate posology in each clinical setting. Different HES formulations (130/0.4 vs. 200/0.5) should be considered as well.

Please consider (and discuss) in your response other available treatment options, i.e. other colloid solutions and crystalloid solutions.

Question No. 5

Provide a full benefit/risk assessment of your HES containing medicinal product, solution for infusion in the currently approved indication(s) in the EU. In addition to patients with sepsis and renal impairment, other groups at potentially increased risk of adverse events, such as patients with head injury and organ donors, should be specifically discussed.

Please consider for your response the results of all relevant studies, including the following:

- *CRYSTMAS, 2012, 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; (UK)*
- *CHEST, 2012, Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care;* The potential signal of increased hepatic organ failure seen in this study should be discussed. Meta-analysis methods should be used, as appropriate.
- *6S, 2012, Hydroxyethyl Starch 130/0.4 vs. Ringer's Acetate in Severe Sepsis*;
- *VISEP, 2008, Intensive insulin therapy and pentastarch resuscitation in severe sepsis*.

Question No. 6

Please comment on the adequacy of the current risk minimisation measures for HES-containing medicinal products, solution for infusion, particularly in the following populations:

a) patients with renal insufficiency;

b) patients with sepsis, with particular regard to potentially increased overall mortality; Please include any distinction between patients with “sepsis” and “severe sepsis”;

c) patients with sepsis and renal insufficiency dependent on dialysis;

d) critically ill patients with particular regard to potentially increased risk of need for renal replacement therapy;

The response to the above requested should give due consideration as to:

- whether there is an estimated glomerular filtration rate (eGFR) below which HES containing medicinal products should not be used;
- whether there is a need for modifying the posology according to the RIFLE classification, where renal injury is considered prior to development of renal failure;
- the effects of other nephrotoxic agents that are commonly co-administered in sepsis, for example aminoglycosides, vancomycin, amphotericin and CT contrast agents, and the potential interaction;
- HES-containing medicinal products and the concomitant use of inotropes (e.g. norepinephrine, vasopressin, epinephrine, dobutamine, dopamine) on renal function;

Question No. 7

In addition, where appropriate, please provide proposals and justification with supportive evidence for any measures to further minimise the risks including changes to the SPC and package leaflet.