European Medicines Agency recommends the suspension of infusion solutions containing Hydroxyethyl Starch

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Information on Medicinal Product

Infusion solutions containing Hydroxyethy-starch (HES) are medicines mainly used to replace lost blood volume in hypovolaemia (low blood volume caused by dehydration or blood loss) and hypovolaemic shock (a steep fall in blood pressure caused by drop in blood volume). They are used in critically ill patients including patients with sepsis (bacterial infection of the blood) or burn or trauma injuries, or patients who are undergoing surgery. There are two main types of medicines used for volume replacement: crystalloids and colloids. Colloids contain large molecules such as starch, whereas crystalloids, such as saline (salt) solutions or Ringer acetate, contain smaller molecules. Infusion solutions containing HES belong to a class known as colloids. In the European Union (EU), HES-containing solutions for infusion have been approved via national procedures and are available in all Member States under various trade names. In Malta, the two solutions authorised and marketed are Volulyte 6% Solution for Infusion (Fresenius Kabi) and Plasma Volume Redibag 6% Solution for Infusion (Baxter).

Information from European Medicines Agency about the safety concern

The review of infusion solutions containing HES was triggered by the German medicines agency, the Federal Institute for Drugs and Medical Devices (BfArM), following three recent studies[1,2,3] that compared HES with other products used for volume replacement called crystalloids in critically ill patients. The studies showed that patients with severe sepsis treated with HES were at a greater risk of kidney injury requiring dialysis. Two of the studies[1,2] also showed that in patients treated with HES there was a greater risk of mortality. The PRAC was therefore requested to assess the available evidence and how it impacts on the risk-benefit balance of HES infusion solutions in the management of hypovolaemia and hypovolaemic shock.

The PRAC assessed data from the scientific literature and the data submitted by the companies, and took advice from a group of external experts. The PRAC was of the opinion that, when compared with crystalloids, patients treated with HES were at a greater risk of kidney injury requiring dialysis and had

[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] Brunkhorst, F.M. *et al.* Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med, 2008; 358(2):125-39.
[3] Myburgh, J.A. *et al.* Hydroxyethyl starch or saline for fluid resuscitation in intensive care; N Engl J Med 2012; 367(20):1901-11.

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a greater risk of mortality. The PRAC also considered that the available data only showed a limited benefit of HES in hypovolaemia, which did not justify its use considering the known risks. The PRAC therefore concluded that the marketing authorisations for these medicines be suspended.

Following the PRAC recommendation, three of the MAHs concerned - Fresenius Kabi and Serumwerk Bernburg AG and B. Braun Melsungen - have requested a re-examination of the PRAC recommendation. While the re-examination is ongoing, some Member States have taken action to suspend or limit the marketing or use of these medicines in their territories pending the outcome of the re-examination. Healthcare professionals in Malta are advised that the outcome of the commission decision is awaited prior to taking any regulatory decisions.

The PRAC is now also considering whether there is a need for regulatory action across the EU while the re-examination is being conducted. For more information please visit the European Medicines Agency (EMA's) website on www.ema.europa.eu

Reporting Adverse Drug Reactions

Healthcare professionals are encouraged to maintain vigilance on colloid infusion solutions containing Hydroxyethyl-starch. Suspected Adverse Drug Reactions (side effects) may be reported using the Medicines Authority yellow card scheme or online at **http://www.medicinesauthority.gov.mt/adrportal** or to the marketing authorisation holder or their local representatives.>

Dr John J Borg PhD (Bristol)

Post-licensing director

Healthcare professionals and patients are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.

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