



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 July 2018
EMA/498908/2018

Hydroxyethyl starch solutions: CMDh introduces new measures to protect patients

Medicines to remain on the market provided that training, controlled access and warnings on the packaging are implemented

On 27 June 2018, the CMDh¹ decided that hydroxyethyl starch (HES) solutions for infusion should remain on the market provided that a combination of additional measures to protect patients is implemented. This followed further reflection, in consultation with EU Member States, on whether it would be feasible to introduce new measures that would effectively reduce the risks with these medicines.

HES solutions for infusion are used to replace plasma volume following acute (sudden) blood loss, where treatment with alternative products known as 'crystalloids' alone is not considered sufficient.

In January 2018, EMA's safety committee PRAC recommended suspending the marketing authorisations of these medicines because they continued to be used in critically ill patients and patients with sepsis despite restrictions introduced in 2013 due to the risk of kidney injury and death in these patients.

The CMDh agreed with the PRAC's assessment of the serious risks in critically ill patients and patients with sepsis. However, the CMDh gave further consideration to the place of HES in the clinical practice of some countries, noted that previous risk minimisation measures had some effect, and considered that a combination of new risk minimisation measures would effectively ensure that HES solutions are not used in patients at risk.

The new measures are:

- the implementation of a controlled access programme by the companies holding the marketing authorisations to ensure that only accredited hospitals will be supplied with these medicines. The accreditation would require that relevant healthcare professionals receive training on the safe use of HES solutions for infusion. Further details about the training and the controlled access programme will be provided to hospitals and healthcare professionals in due time;
- warnings in the medicines' packaging and at the top of the summaries of product characteristics (SmPCs) reminding healthcare professionals that these medicines must not be used in patients with sepsis or kidney impairment or in critically ill patients;

¹ The CMDh is a medicines regulatory body representing the European Union (EU) Member States, Iceland, Liechtenstein and Norway.



- writing directly to healthcare professionals to ensure that they are fully aware of the conditions of use of the medicines and the groups of patients that must not receive them due to an increased risk of kidney injury and death.

The CMDh also requested marketing authorisation holders to conduct studies to check that only patients who should be treated with these medicines are receiving them. This is in addition to ongoing studies on the benefits and risks of HES solutions in patients with trauma and those undergoing elective surgery.

The CMDh position was adopted by majority vote and the matter was sent to the European Commission, which took an EU-wide legally binding decision on 17 July 2018.

Information for patients

- HES solutions for infusion are used to replace fluids in the body after acute (sudden) blood loss.
- Because of the risk of kidney injury and death, HES solutions for infusion must not be used in patients with blood infection or kidneys problems or in critically ill patients.
- If you are given a HES infusion, your doctor will monitor your kidneys to check that they are working well enough.
- Patients who have questions or concerns should speak to their treating doctor.

Information for healthcare professionals

- Because of the risk of kidney injury and mortality, HES solutions for infusion are contraindicated in patients with **sepsis or in critically ill patients**.
- HES solutions for infusion should be used for managing hypovolaemia due to acute blood loss only when crystalloids alone are not considered sufficient. HES solutions should not be used for fluid maintenance.
- Use of HES solutions for infusion should be restricted to the initial phase of volume resuscitation with a maximum time interval of 24 hours. Treatment should be guided by continuous haemodynamic monitoring so that the infusion is stopped as soon as haemodynamic goals have been achieved.
- Additional studies are ongoing with HES solutions in patients with trauma and those undergoing elective surgery to further investigate the long-term safety of HES prescribed according to the recommendations for use (dose less than 30 ml/kg and duration less than 24 hours).
- The expected benefit of treatment should be carefully weighed against the uncertainties with regard to long-term safety.
- Alternative therapeutic options are available for routine clinical practice and should be considered according to relevant clinical guidelines.
- HES solutions for infusion are contraindicated in patients with **renal impairment or undergoing renal replacement therapy**. The use of HES must be discontinued at the first sign of renal injury. An increased need for renal replacement therapy has been reported up to 90 days after HES administration. Patients' kidney function should be monitored after HES administration.

- HES solutions for infusion are contraindicated in **severe coagulopathy**. HES solutions should be discontinued at the first sign of coagulopathy. Blood coagulation parameters should be monitored carefully in case of prolonged use.
- HES solutions for infusion are also contraindicated in **dehydrated patients, hyperhydrated patients, patients with intracranial or cerebral haemorrhage, burn injuries, severe hyperkalaemia, hypernatraemia, hyperchloraemia, congestive heart failure, organ transplant patients and patients with impaired hepatic function**.

Healthcare professionals will be informed in writing of the outcome of the review and the introduction of the new risk minimisation measures, which include the introduction of a controlled access programme requiring training of relevant healthcare professionals on the safe use of these medicines. This programme will be implemented by the companies holding the marketing authorisations. Further details about the training and the controlled access programme will be provided to hospitals and healthcare professionals in due time.

More about the medicine

HES solutions for infusion are used for the management of hypovolaemia (low blood volume) caused by acute blood loss, where treatment with alternative infusion solutions known as ‘crystalloids’ alone is not considered sufficient. They are given by infusion (drip) into a vein and are used as blood volume expanders to prevent a dangerous drop in blood pressure following acute bleeding. They belong to the class of medicines known as colloids. Besides blood products, there are two types of medicines used for plasma volume replacement: crystalloids and colloids. Colloids contain large molecules such as starch, whereas crystalloids, such as saline or Ringer’s solutions, are electrolyte solutions.

In the European Union, HES solutions for infusion have been approved via national procedures and are available in the Member States under various trade names.

More about the procedure

The review of HES solutions for infusion was initiated on 17 October 2017 at the request of the Swedish Medical Products Agency, under [Article 107i of Directive 2001/83/EC](#).

The review was first conducted by the Pharmacovigilance Risk Assessment Committee (PRAC), EMA’s Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations on 12 January 2018. The PRAC recommendations were sent to Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which adopted a position on 24 January 2018. The CMDh, a body representing EU Member States, is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.

As the CMDh position was adopted by majority vote, it was sent to the European Commission. In April 2018, the European Commission requested that the PRAC and the CMDh further consider any possible unmet medical need that could result from a suspension, as well as the feasibility and likely effectiveness of additional risk minimisation measures.

After looking at these specific aspects, in May 2018 the PRAC confirmed its previous recommendation for suspension and sent a revised recommendation to the CMDh. In June 2018, the CMDh concluded

that HES solutions for infusion should remain on the market provided that a combination of additional measures to protect patients is implemented.

As the CMDh position was adopted by majority vote, the CMDh position was sent back to the European Commission, which took an EU-wide legally binding decision on 17 July 2018.