Article 107i of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-107i/1457

Solutions for infusion containing hydroxyethyl starch (HES)

Divergent statement

The undersigned CMDh members disagree with the CMDh position that the marketing authorisations for HES solutions for infusion should be maintained on the market, with additional risk minimisation measures.

This position of the CMDh goes against the scientifically based recommendations of the PRAC to suspend the marketing authorisation of HES solutions for infusion.

In 2013, the PRAC concluded in reviews under article 31 of Directive and Article 107i of Directive 2001/83/EC that HES solutions for infusion are associated with an increased risk of mortality and renal failure in patients with sepsis or critical illness. The benefit-risk balance of HES was found to be positive only in a restricted indication, and on the condition that the patient populations at known risk of serious harm could be adequately protected from exposure to HES solutions for infusion by the imposed risk minimisation measures. No new data since this review have become available that change the conclusions regarding efficacy and safety from the previous 2013 referral including that the benefits of HES solutions for infusion do not outweigh the serious risks in patients with sepsis or critical illness.

The results from two separate drug utilisation studies, which were imposed to assess the effectiveness of the risk minimisation measures implemented as an outcome of the 2013 referral, have been reported by two MAHs in 2017. The undersigned agree with the PRAC conclusion that these studies are representative of the clinical usage in the European Union, and that key results are reliable. The results indicate that the implemented restrictions in use are not adhered to. Overall non-adherence to the revised product information was reported to be high, and PRAC was particularly concerned that approximately 9% of patients exposed to HES solutions for infusion were critically ill, approximately 5-8% of patients had renal impairment and approximately 3-4% of patients had sepsis.

It should be acknowledged that the main concern is use in a previously approved indication, where restriction (contraindications) has been implemented due to strong evidence of serious harm in terms of mortality and renal injury requiring renal replacement therapy. Conservative estimates using the drug utilisation study results and EU exposure data are that tens of thousands of patients with sepsis and tens of thousands of critically ill patients have been exposed to HES solutions for infusion annually in the EU since the previous referral procedure. Combined with the increased risks seen in large randomised controlled trials, this is considered unacceptable, in terms of levels of attributable mortality and clinical harm in these patients. While these estimates have uncertainties and therefore should be interpreted cautiously, it provides an important notion of the magnitude of the risk. In the overall benefit-risk balance for HES solutions for infusion, this should consequently be outweighed by a benefit of sufficient (i.e. substantial) magnitude. No such benefit is documented, could be expected, and will not, according to the CHMP advice provided, be possible to show in the ongoing RCTs in the approved indication. The benefit-risk balance for use in the approved indication remains conditional on protecting populations, where serious harm has been reliably demonstrated, from exposure to HES. Sufficient protection of vulnerable populations is currently not provided.

It is a particular concern that the patient populations that have been clearly identified at risk for increased mortality and renal injury from exposure to HES solutions for infusion, patients with sepsis and critically ill patients, are particularly vulnerable:

They are severely ill, often in a critical condition. They are not informed of the decision to use HES, and have no opportunity to consider if they are willing to accept an increased risk for mortality or renal injury from this treatment selection.

They have no opportunity for a treatment benefit, since the expected ultimate benefit from treatment of hypovolemia is a reduction of renal injury and mortality. Randomised controlled trials show the opposite outcome. Further, not even a volume-sparing effect is seen in the 6S trial or the CHEST trial compared to treatment with crystalloids.

The term 'unmet medical need' should indicate a defined population where there is evidence that the outcome would be worse with available alternative treatments, if HES solutions for infusion are not available. The potential for an unmet medical need in a population within the current indication in the event of a suspension has not been adequately demonstrated. No member state has been able to define a population for whom this would be an issue. Several member states have described 'unmet medical' need in terms of clinician preference, including in off-label indications; these are not considered representative of an unmet medical need. Whilst the *ad-hoc* expert group in their meeting in December 2017 concluded that there was 'a place' for HES products in patients with hypovolaemia, they only defined a potential unmet medical need in off-label indications such as plasmapheresis and patients in shock with contraindications to other colloids and who are also refractory to treatment with crystalloids. This population is considered to be vanishingly rare, and as such does not constitute an unmet medical need requiring the continued availability of HES solutions for infusion. The focus for the regulatory conclusion in the referral procedure should be on the overall benefit-risk balance.

The PRAC carefully considered all options for measures to further mitigate these risks as proposed by MAHs and Member States, both as individual measures and in combination. The following risk minimisation measures were considered in detail: changes to the product information, direct health care professional communication, educational materials, warning on the primary container of the products, sign-in for medication form, prescription sheet or checklist, restricted access and distribution system to accredited hospitals or physicians. It is important to note that the results from the DUSs show that despite measures taken in 2013, satisfactory risk minimisation has not been achieved for risks of increased mortality and renal injury involving a large number of patients, and that available evidence shows that the non-adherence is not solely due to a lack of awareness of the restrictions by prescribers, rendering further communication and education unlikely to be sufficiently effective. The sign-in for medication form, prescription sheet or checklist would also raise feasibility issues in an emergency setting. Regarding the proposed restricted access/distribution program, there is no evidence provided that this will be possible to implement across EU member states, and is therefore seriously questioned. In conclusion no additional risk minimisation measures or combination of risk minimisation measures, to ensure safe and effective use of HES solutions for infusion could be identified. Additionally, in Member States where usage has decreased significantly the implementation of extensive educational programmes has the potential to be promotional and therefore could increase, rather than reduce, risks associated with these products. This may also be the case in other Member States irrespective of usage.

Thus, the undersigned CMDh members consider the benefit/risk balance for solutions for infusion containing hydroxyethyl starch (HES) to be negative.

CMDh Members expressing a divergent opinion:

Andrzej Czesławski (PL)	27 June 2018
Christin Olofsson (SE)	27 June 2018
Jascha Johann Hörnisch (AT)	27 June 2018
Katrine Damkjær Madsen (DK)	27 June 2018
Keith McDonald (UK)	27 June 2018
Lyudmil Antonov (BG)	27 June 2018
Margit Plakso (EE)	27 June 2018
Maria Vitocolonna (IT)	27 June 2018
Monta Emersone (LV)	27 June 2018
Nicole Kavanagh (IE)	27 June 2018
Paulina Ikäheimo (FI)	27 June 2018
Žydrūnas Martinėnas (LT)	27 June 2018

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CMDh Members expressing a divergent opinion:

Orn Gudmundsson (IS)	27 June 2018
Suzanne Collett Gordon (NO)	27 June 2018