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Guido Rasi, M.D.
Executive Director
European Medicines Agency
30 Churchill Place
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London E14 5EU
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Sent to: guido.rasi@ema.europa.eu

Dear Dr. Rasi,

We are writing to urge you to withdraw the European Medicines Agency's (EMA's) approval of all hydroxyethyl starch (HES) intravenous solutions from the European market because the solutions cause kidney failure, bleeding, and increased risk of death, and there are numerous safer intravenous fluids that are just as effective and are available in Europe. Today, Public Citizen filed a petition with the U.S. Food and Drug Administration (FDA) requesting that the FDA ban HES solutions in the U.S. Public Citizen is joined in the petition by two internationally recognized experts on critical care medicine, including the dangers of HES: Dr. Charles Natanson, critical care physician in the U.S., and Dr. Ian Roberts, editor of the Cochrane Injuries Group and Co-Director of the Clinical Trials Unit at the London School of Hygiene & Tropical Medicine. A copy of the petition, which we hope you will review, is enclosed.

The petition offers a point-by-point rebuttal, supported by an exhaustive review of the scientific literature, of the various arguments offered by the producers of HES solutions and others for keeping the products on the market. The petition also explains that HES solutions offer no unique benefit over the other types of intravenous solutions on the market and that there is therefore no compelling reason to continue to expose patients to the unique risks of HES products.

History of HES dangers and FDA response

As you know, HES solutions have been marketed since 1972 as an option for treating patients who need IV solutions to maintain or increase their fluid volume.[1] Yet, beginning right after

[1] Food and Drug Administration. September 23, 2014 Pediatric Advisory Committee memorandum. NDA BN070012: Voluven. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM414088.pdf. Accessed January 4, 2017.

HES solutions came on the market, evidence began to emerge that they could impede the blood's ability to clot properly[2] and were stored in body tissues long after they were administered.[3] Beginning in 2008, pivotal evidence began to emerge that even more definitively demonstrated the dangers of HES products. Over the next four years, three large multicenter randomized clinical trials were published showing increased rates of renal failure, bleeding, and mortality associated with HES solution use in critically ill patients, including those with sepsis.[4,5,6,7] That such evidence came to light only after the solutions were approved was not surprising, given that their approval was based on small, short, and poorly designed clinical trials.[8]

In 2013, the FDA issued a safety alert warning doctors and patients of these side effects and warned against using HES solutions in critically ill patients, including those with sepsis because of the increased risk of death and kidney damage.[9] However, the agency, with no justification, allowed the solutions to continue to be used in other patients, including those undergoing major surgery, despite evidence showing that HES solutions had the same dangers in all patients.

European Medicines Agency response: initially correct decision, reversed

In June 2013, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) recommended that the marketing authorizations for HES products be suspended because its review found that the benefits of HES solutions no longer outweighed their risks.[10] The PRAC stated the following in explaining its decision:[11]

> 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 a greater risk of mortality.

The PRAC further noted "that the **available data only showed a limited benefit of HES in hypovolaemia**, which did not justify its use considering the known risks" [emphasis added]. It is

[2] Alexander B, Odake K, Lawlor D, Swanger M. Coagulation, hemostasis, and plasma expanders: a quarter century enigma. *Fed Proc*. 1975;34(6):1429-1440.
[3] Bellmann R, Feistritzer C, Wiedermann CJ. Effect of molecular weight and substitution on tissue uptake of hydroxyethyl starch: a meta-analysis of clinical studies. *Clin Pharmacokinet*. 2012;51(4):225-236.
[4] Hartog CS, Natanson C, Sun J, et al. Concerns over use of hydroxyethyl starch solutions. *BMJ*. 2014;349:g5981.
[5] Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012;367(20):1901-1911.
[6] Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med*. 2008;358(2):125-139.
[7] Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med*. 2012;367(2):124-134.
[8] Hartog CS, Natanson C, Sun J, et al. Concerns over use of hydroxyethyl starch solutions. *BMJ*. 2014;349:g5981.
[9] Food and Drug Administration. FDA safety communication: boxed warning on increased mortality and severe renal injury, and additional warning on risk of bleeding, for use of hydroxyethyl starch solutions in some settings. November 25, 2013. http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm358271.htm. Accessed January 5, 2017.
[10] European Medicines Agency. PRAC recommends suspending marketing authorisations for infusion solutions containing hydroxyethyl starch. June 14, 2013. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/06/news_detail_001814.jsp&mid=WC0b01ac058004d5c1. Accessed January 4, 2017.
[11] *Ibid.*

noteworthy that the PRAC did not find any compelling evidence that the benefit-risk profile of HES solutions was different in surgical and trauma patients, concluding that HES products should remain banned "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**" [emphasis added].

However, several HES solution manufacturers requested a re-examination of this PRAC recommendation.[12] In addition, the United Kingdom's Medicines and Healthcare products Regulatory Agency notified the EMA member states of its consideration of the need to remove HES solutions from the U.K. market.[13] Because of both of these actions, a second PRAC committee was convened to reanalyze the evidence. In October 2013, the committee reversed the initial recommendation to completely ban HES solutions and recommended that HES solutions remain on the market for use "in patients with hypovolemia caused by acute blood loss where treatment with alternative infusions [*sic*] solutions known as 'crystalloids' alone are not considered to be sufficient."[14]

Only 19 of the 33 committee members, however, voted to reverse the original decision.[15] The 14 dissenting members articulated their arguments for maintaining the original decision to ban HES solutions in documents known as "divergent statements" at the end of the EMA's publicly released review of its decision (see Appendix 1 of enclosed petition).[16] These 14 members based their decision on four main arguments:

- First, that "the evidence to demonstrate a lower risk of renal injury and mortality in any settings other than sepsis and the critically ill is weak."
- Second, that "the data evaluating benefit in the perioperative setting and trauma setting do not adequately support a clinically relevant beneficial effect for HES."
- Third, that there exists "an overlap between those patient groups where the benefit-risk balance of HES is judged to be negative (septic and critically ill patients), and the patients who will receive HES under the revised indication allowing use in patients with hypovolaemia due to acute bleeding (e.g. including the trauma and perioperative settings)."

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[12] European Medicines Agency. Assessment report for solutions for infusion containing hydroxyethyl starch. November 11, 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Hydroxyethyl_starch-containing_medicines_107/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500154254.pdf. Accessed January 4, 2017. PDF pp. 3-4.

[13] *Ibid*.

[14] European Medicines Agency. PRAC confirms that hydroxyethyl-starch solutions (HES) should no longer be used in patients with sepsis or burn injuries or in critically ill patients. October 11, 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Solutions_for_infusion_containing_hydroxyethyl_starch/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500151963.pdf. Accessed January 5, 2017.

[15] Hartog CS, Natanson C, Sun J, et al. Concerns over use of hydroxyethyl starch solutions. *BMJ*. 2014;349:g5981.

[16] European Medicines Agency. Assessment report for solutions for infusion containing hydroxyethyl starch. November 11, 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Hydroxyethyl_starch-containing_medicines_107/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500154254.pdf. Accessed January 4, 2017. PDF pp. 36-38, 40-41.

- Fourth, that "[t]he mechanism underlying the risks of renal injury and mortality observed with HES is not well understood, and therefore these should be considered to be potential risks in all patient groups."

Both old and new evidence overwhelmingly point to dangers of HES solutions in all patients

We agree with the 14 PRAC members who, based on the evidence that existed at the time of the 2013 decision, argued against the reversal of the decision to ban HES products in Europe. Since the PRAC reversal of its original decision, even more evidence has emerged that confirms the dangerous side effects of HES solutions and the absence of any unique benefit of HES solutions compared with other intravenous fluids. As detailed in our petition, this evidence includes two meta-analyses of clinical trials[17,18] and seven observational studies[19,20,21,22,23,24,25] in surgical and trauma patients. The studies replicated the findings of earlier studies of the increased risks posed by HES solutions compared with other intravenous fluids. The EMA's and FDA's distinction between critically ill patients (for whom HES is no longer recommended) and those undergoing major surgery or suffering from trauma (to whom the agencies allowed HES to continue to be marketed) is entirely arbitrary and not supported by any solid evidence.

As you may recall, in response to the PRAC's October 2013 decision to reverse the ban, 76 internationally recognized researchers in intensive care and other disciplines in 2014 sent you an open letter expressing concern about the PRAC's decision and the risk of harm to which patients treated with HES products would be exposed (see Appendix 2 of enclosed petition).[26] They posed the following fundamental question to the PRAC: "What assumptions or clinical data would indicate that the same pathological mechanisms do not apply in patients with hypovolaemia from blood loss?" These researchers also pointed out that the PRAC's recommendations to monitor kidney function in patients for at least 90 days after HES solution

[17] Wilkes MM, Navickis RJ. Postoperative renal replacement therapy after hydroxyethyl starch infusion: a meta-analysis of randomised trials. *Neth J Crit Care.* 2014;18(4): 4-9.
[18] Raiman M, Mitchell CG, Biccard BM, Rodseth RN. Comparison of hydroxyethyl starch colloids with crystalloids for surgical patients: A systematic review and meta-analysis. *Eur J Anaesthesiol*. 2016;33(1):42-48.
[19] Allen CJ, Valle EJ, Jouria JM, et al. Differences between blunt and penetrating trauma after resuscitation with hydroxyethyl starch. *J Trauma Acute Care Surg*. 2014;77(6):859-864.
[20] Kashy BK, Podolyak A, Makarova N, et al. Effect of hydroxyethyl starch on postoperative kidney function in patients having noncardiac surgery. *Anesthesiology*. 2014;121(4):730-739.
[21] Patel MS, Niemann CU, Sally MB, et al. The impact of hydroxyethyl starch use in deceased organ donors on the development of delayed graft function in kidney transplant recipients: A propensity-adjusted analysis. *Am J Transplant*. 2015;15(8):2152-2158.
[22] Ahn HJ, Kim JA, Lee AR, et al. The risk of acute kidney injury from fluid restriction and hydroxyethyl starch in thoracic surgery. *Anesth Analg*. 2016;122(1):186-193.
[23] Lagny MG, Roediger L, Koch JN, et al. Hydroxyethyl starch 130/0.4 and the risk of acute kidney injury after cardiopulmonary bypass: A single-center retrospective study. *J Cardiothorac Vasc Anesth*. 2016;30(4):869-875.
[24] Albrecht FW, Glas M, Rensing H, et al. A change of colloid from hydroxyethyl starch to gelatin does not reduce rate of renal failure or mortality in surgical critical care patients: Results of a retrospective cohort study. *J Crit Care*. 2016;36:160-165.
[25] Eriksson M, Brattström O, Mårtensson J, Larsson E, Oldner A. Acute kidney injury following severe trauma: Risk factors and long-term outcome. *J Trauma Acute Care Surg*. 2015;79(3):407-412.
[26] Bellomo R, Bion J, Finfer S, et al. Open letter to the Executive Director of the European Medicines Agency concerning the licensing of hydroxyethyl starch solutions for fluid resuscitation. *Br J Anaesth*. 2014;112(3):595-600.

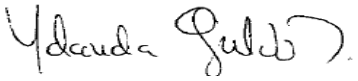
administration and not to use HES solutions for longer than 24 hours are insufficient to prevent adverse effects.

Original PRAC decision to ban HES must be reinstated to protect patients, save lives

It is imperative that you immediately direct the PRAC to convene again and revisit the evidence in existence at the time of the 2013 reversal of its decision to ban HES solutions and evidence that has emerged since that time that confirms the dangers of HES. We are confident that the PRAC would vote, once again, to ban HES solutions from the European market, thus saving many patients from harm and death.

We look forward to a prompt reply to this urgent letter.

Sincerely,



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Enclosure