EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Yolanda Giraldo, Resident, General Preventive Medicine Johns Hopkins School of Public Health
Sammy Almashat, Researcher, Public Citizen's Health Research Group
Sidney Wolfe, Founder and Senior Adviser, Public Citizen's Health Research Group
Michael Carome, Director, Public Citizen's Health Research Group
Charles Natanson, Critical Care Physician
Ian Roberts, Co-ordinating Editor, Cochrane Injuries Group, Co-Director, Clinical Trials Unit, London School of Hygiene & Tropical Medicine

9 March 2017
EMA/124548/2017
Human Medicines Evaluation Division

Dear Madam/Sir,

Subject: Hydroxyethyl starch solutions

Thank you for your letter dated 8 February 2017 requesting the European Medicines Agency (EMA) to reconsider its conclusions of 2013 related to medicinal products for solutions for infusion containing hydroxyethyl starch (HES), through the Pharmacovigilance Risk Assessment Committee (PRAC). EMA welcomes interaction with stakeholders and is grateful to you for bringing your concerns to our attention.

The PRAC, within its mandate of the assessment of risk management of human medicines, monitors the safety profile and assesses continuously the benefit-risk balance of all human medicinal products throughout their life-cycle. A number of regulatory tools can be used to this effect, including European Union (EU)-wide reviews, safety signal detection activities, periodic safety update reports (PSURs) and post-authorisation safety studies.

For HES, as pointed out in your letter, two EU-wide reviews were concluded in 2013, namely a review under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1348) and an urgent Union review under Article 107i of Directive 2001/83/EC (EMEA/H/A-107i/1376)[1]. In the urgent Union review, the PRAC considered data assessed in the review under Article 31 as well as data not available for assessment at the time of this previous review. Thus, all data available at the time, in particular with regards to the risk of mortality and renal injury, were considered in the urgent Union review including data from clinical studies, meta-analyses of clinical studies, post-marketing experience, responses submitted by the marketing authorisation holders (MAHs) in writing and during oral explanations and stakeholders' submissions (e.g. from members of the public including healthcare professionals). The PRAC also considered the views of clinical experts sought through two ad-hoc experts group meetings.

[1] Should you require further information concerning the Article 31 and Article 107i procedures mentioned above (including the assessment reports on HES containing medicinal products and annex IV describing the conditions to the marketing authorisation), please refer to the EMA's website pages dedicated to these procedures (under the "all documents" tab):
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Hydroxyethyl_starch-containing_solutions/human_referral_prac_000012.jsp&mid=WC0b01ac05805c516f
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Hydroxyethyl_starch-containing_medicines/human_referral_prac_000029.jsp&mid=WC0b01ac05805c516f

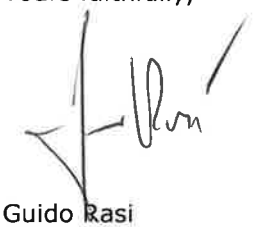
The PRAC then concluded that the use of HES products should be restricted to the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient, subject to restrictions, contraindications, warnings and other changes to the product information. A Direct Healthcare Professional Communication was also issued to inform healthcare professionals of the outcome of this review and restrictions to the use of HES-containing medicinal products. The marketing authorisations for these medicinal products were amended accordingly.

The PRAC also recommended further studies to be conducted in order to provide more evidence on the efficacy and safety of hydroxyethyl starch. These studies were imposed as conditions to the marketing authorisation and include two randomised clinical trials in perioperative and trauma settings to further evaluate the efficacy and safety of HES solutions and a drug utilisation study to evaluate the effectiveness of the risk minimisation measures taken. The protocols of these studies were assessed by the relevant competent authorities (PRAC/national competent authority) to ensure that they are suitably designed and results will be assessed as they become available.

In addition, since 2013 the MAHs of HES products have submitted two safety update reports (PSURs) considering the period up to March 2016. These reports were assessed and reviewed by the PRAC which concluded that the benefit-risk of these HES products remains favourable when used in accordance with the terms of the marketing authorisations. Data up to March 2017 will be considered as part of the next PSURs which are due to be submitted for assessment to EMA and the EU Member States in May 2017. Hence, the majority of data that emerged since the completion of the EU reviews in 2013 referenced in your letter have been reviewed in this context. Any remaining data referenced in your letter will be reviewed as part of the assessment of the upcoming PSURs.

Therefore, please rest assured that the European regulatory system is continuously monitoring the safety of HES products, taking into consideration any new evidence that becomes available.

Yours faithfully,



Guido Rasi
Executive Director