**CMDh DIVERGENT POSITION**

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Procedure No: EMEA/H/N/PSR/J/0031

hydroxyethyl starch (HES) solutions for infusion

**Divergent statement**

The undersigned member(s) of the CMDh did not agree with the PRAC's positive recommendation recommending the suspension of the nationally authorised medicinal product(s) containing hydroxyethyl starch (for details see PRAC assessment report).

The reason for divergent opinion was the following:

A Joint Drug Utilisation Study (JDUS) was submitted in fulfilment of conditions to the marketing authorization following procedure EMEA/H/A-107i/1457. This study assessed the effectiveness of the new set of risk minimisation measures (RMMs) on the non-adherence to the approved European PI regarding indication, contraindication and posology. The JDUS recruited 1851 patients fulfilling the study eligibility criteria for 1863 prescriptions in 32 sites/hospitals across European countries.

The results of the JDUS show that there was a reduction in overall non-adherence to 23.91% compared to 69% - 77.5% in previous DUSs mandated, following the previous EU Article 31 (EMEA/H/A-31/1348) and 107i (EMEA/H/A-107i/1376) referral procedures.

An 18.85% of non-adherence pertained to indications which was driven specifically by high non-adherence rates observed in some MSs (BE 94%, IT 81%, NL 85% and FR 39.9%) as compared to DE 5.7%, PL 26%, ES; CZ & HU, with less than 20% of non-adherence. Although the results suggest that the RMMs are not well fitted to all countries/sites, they have worked quite well in some other countries. The further measures proposed by the MAHs in this procedure aim at improving the non-adherence of practitioners related to the currently implemented controlled access program, are expected to leave a huge impact on the practice and are sufficient to counteract the diffuse practice of off-label use. These measures are focused not only on raising awareness of HCPs but also on the prevention of product delivery to departments that previously administered HES incorrectly as well as on the restriction of delivery (by hospital pharmacies) of HES-containing product to Anaesthesia and Emergency departments only. The re-certification of centers will limit the use of the product only where acute blood loss occurred, thereby further improving adherence to the PI.

Key to the benefit-risk for Poly(O-2-hydroxyethyl) starch (HES) are also consideration of the following:

The results of the JDUS show that the median HES dose was 500 mL (6.76 mL/kg), and that the median treatment duration was 0.583 hours with almost all patients receiving only a single prescription. Therefore, this short duration of use as seen in the JDUS results has a minimal risk of kidney injury. In addition, the results of non-adherence to contraindications of 6.5% (significantly decreased compared to the results of previous DUS) could be further minimized by the MAHs' proposals. Also, the proposals of the MAHs further reassure that the concerns raised in the Art. 31 referral in 2012 (EMEA/H/A-31/1348) and in Art.107i referral in 2013 (EMEA/H/A-107i/1376) are being effectively resolved.

Moreover, when assessing the B/R profile of HES, the results of DUS should be further completed with all other new information. After the assessment of the last PSUSA for HES in November 2021 (PSUSA 00001694/202103) the PRAC agreed on unchanged B/R profile (i.e. positive). Since that

time, based on available information from published studies and ADR reports, no new important safety information was identified that could modify the current benefit/risk balance.

It is considered that the suspension of marketing authorisation of HES-containing medicinal products is currently not risk proportionate and could lead to an unmet medical need in some severe hypovolemic situations.

Therefore, taking into account the results obtained within the framework of the DUS together with all other available information on safety and efficacy, the benefit-risk balance of the HES products remains unchanged.

**CMDh Members expressing a divergent opinion:**

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| Cristian Georgescu | 24 February 2022 |
| Eleftheria Nikolaidi | 23 February 2022 |
| Jitka Vokrouhlická | 23 February 2022 |
| Magdolna Németh | 23 February 2022 |
| Mathilde Geynet | 24 February 2022 |
| Miroslava Petriková | 23 February 2022 |
| Nevenka Prpar | 23 February 2022 |
| Verónica García Morales | 23 February 2022 |