<Date>

Hydroxyethyl starch (HES) solutions for infusion: suspension of marketing authorisations due to continued use in contraindicated patient populations with increased risk of serious harm

<Brand names to be completed nationally>

Dear Healthcare professional,

Fresenius Kabi and B Braun in agreement with the European Medicines Agency and the <National Competent Authority > would like to inform you of the following:

Summary

- **In 2013 the use of HES solutions for infusion was restricted because of an increased risk of kidney injury and mortality in certain patient populations.**
- **Despite extensive measures in place to protect vulnerable patient populations, final results of a drug utilisation study have shown continued high non-adherence to the product information including non-adherence to contraindications.**
- **No further measures have been identified to further improve adherence and mitigate these risks which exposes patients to potential serious harm, including increased mortality.**
- **As a consequence, HES solutions for infusion have now been suspended from the EU market.**
- **Healthcare professionals should no longer use HES solutions for infusion and consider other appropriate treatment alternatives according to relevant clinical guidelines.**
- **<Recall information, if applicable, including level (pharmacy) and date of recall>**

Background on the safety concern

Hydroxyethyl starch (HES) solutions for infusion are artificial colloids for volume replacement and are currently indicated for the treatment of hypovolemia due to acute blood loss when crystalloids alone were not considered sufficient.

HES containing products have been the subject of several European assessments of their benefit-risk balance over years.

In October 2013, a safety review was completed about an increased risk of kidney dysfunction and mortality in patients with sepsis or critical illness in large randomised clinical trials. The review concluded to restrict the use of HES solutions for infusion to the current indication. The product information was updated, including new contraindications and warnings.

In October 2017, an additional review of the results of two drug utilisation studies (DUSs) was performed. These studies raised concerns because key restrictions are not adhered to in clinical practice and that there was use in contraindicated populations.

Subsequently, in 2018, additional measures have been put in place to reinforce adherence to the authorised conditions of use, including restricting supply of HES solutions for infusion only to hospitals/centres where healthcare professionals expected to prescribe or administer them have undergone a mandatory training on the appropriate conditions of use (i.e. a controlled access programme), and more prominent warnings on the packaging of these solutions. Physicians were advised not to use HES solutions for infusion outside the terms of the marketing authorisation as detailed in the summary of product characteristics (SmPC) as this could result in serious harm to their patients.

The marketing authorisation holders were requested to conduct an additional DUS to check adherence to the product information, and to demonstrate the effectiveness of these risk minimisation measures.

In February 2022, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) assessed the final results of this DUS and concluded that non-adherence to the product information remains despite the extensive additional risk minimisation measures implemented in 2018.

PRAC concluded that HES solutions for infusion are still used in contraindicated populations, where there is an increased risk for serious harm, including mortality, and that overall the risks outweigh the benefits for HES-containing products. Marketing of these products should be suspended, and therapeutic alternatives should be selected according to relevant clinical guidelines.

Call for reporting

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Company contact point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	Hydroxyethyl starch (HES) solution for infusion
Marketing authorisation holder(s)	FRESENIUS KABI, B. BRAUN It is expected that a single consistent message is sent to healthcare professionals in each EU Member State. *All concerned marketing authorisation holders in each Member State are strongly encouraged to collaborate, so that a single DHPC is prepared and circulated in each Member State. The letter circulated in each Member State should cover all active substance-containing products authorised in that Member State.* *It is encouraged that the originator marketing authorisation holder (where available) in each Member State acts as the contact point for the national competent authority, on behalf of the other concerned marketing authorisation holders in the same Member State. If no originator product is marketed in the Member State, it is encouraged that one of the concerned generic companies acts as contact point for the competent authority.*
Safety concern and purpose of the communication	Persistent use in contra-indicated populations with increased risk of serious harm. To inform healthcare professionals that the authorisations for hydroxyethyl starch (HES) solution for infusion products has been suspended.
DHPC recipients	Anaesthesiologists, intensive care physicians, hospital pharmacists, emergency care units, further recipients possibly including specialists in infectious diseases, nephrologists, specialists in burn care, specialists in trauma care, obstetricians, nurses, professional societies and national association to be agreed at national level.
Member States where the DHPC will be distributed	All EU Member States where products are authorised/marketed[1,2]

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	10 February 2022
DHPC and communication plan (in English) agreed by CMDh	24 February 2022
Submission of translated DHPCs to the national competent authorities for review	3 March 2022

[1] On 24 May 2022, the European Commission issued a legal decision confirming the suspension of the marketing authorisations of HES solutions for infusion. If necessary for public health reasons, individual EU Member States may delay the suspension for no longer than 18 months and keep HES solutions on the market, subject to agreed risk minimisation measures. The DHPC will only be disseminated in Member States not delaying the suspension.

[2] Update as of 26 July 2022: For further information, please contact the national competent authority in your country of interest.

DHPC COMMUNICATION PLAN	
Agreement of translations by national competent authorities	10 March 2022
Dissemination of DHPC	Within 5 working days of EC decision