<Date>

Hydroxyethyl starch (HES) solutions for infusion ▼: new measures to reinforce existing restrictions due to increased risk of renal dysfunction and mortality in critically ill or septic patients

<Brand names to be completed nationally>

Dear Healthcare professional,

<Name of marketing authorisation holder> in agreement with the European Medicines Agency and the <National Competent Authority > would like to inform you of the following:

Summary

- **Despite restrictions introduced in 2013, drug utilisation studies have shown that HES solutions for infusion have continued to be used in patients with contraindications, including those with sepsis, renal impairment or in critically ill patients. Such contraindicated use is associated with a risk for serious harm, including increased mortality.**
- **In addition restriction in indication is not being fully adhered to either.**
- **HES will be subject to a controlled access programme which will be implemented by Marketing Authorisation Holders. Only accredited hospitals/centres will be supplied with these medicines. The accreditation would require that relevant healthcare professionals who prescribe or administer them receive mandatory training on their safe and effective use.**
- **HES products should only be used for the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient and must not be used in patients with sepsis, renal impairment or in critically ill patients.**
- **A full list of contraindications is included in the product information. These include:**
  - **Sepsis**
  - **Critically ill patients**
  - **Renal impairment or renal replacement therapy**
  - **Dehydrated patients**
  - **Burns**
  - **Intracranial or cerebral haemorrhage**
  - **Hyperhydrated patients, including patients with pulmonary oedema**
  - **Severe coagulopathy**
  - **Severely impaired hepatic function**

Background on the safety concern

An increased risk of kidney dysfunction and mortality in patients with sepsis or critical illness given hydroxyethyl starch (HES) solutions for infusion identified in large randomised clinical trials led to a safety review of these products which was completed in October 2013.

The 2013 review restricted the use of HES solutions for infusion to the treatment of hypovolemia due to acute blood loss when crystalloids alone were not considered sufficient only. In addition new contraindications were implemented in patients with sepsis, in critically ill patients and in renal impairment or renal replacement therapy and the product information was updated with these new contraindications and warnings. The marketing authorisation holders were also required to perform studies to generate further evidence to support the benefit-risk balance in authorised populations

and observational studies to demonstrate that the new restrictions were being followed in clinical practice.

In October 2017, the EMA started a new review of the benefit-risk balance of HES solutions for infusion following the results of two of these observational studies (drug utilisation studies - DUSs). These raised concerns that key restrictions have not been followed in clinical practice and that there is use in contraindicated populations, since 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.

New measures will now be put in place to reinforce adherence in clinical practice to the authorised conditions of use. This will include 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 (controlled access programme), and more prominent warnings on the packaging of these solutions.

Physicians should not 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.

In addition to the above reminders, please note that HES should be used at the lowest effective dose (< 30 ml/kg) for the shortest period of time (< 24 hours). Treatment should be guided by continuous haemodynamic monitoring so that the infusion is stopped as soon as appropriate haemodynamic goals have been achieved.

For full prescribing information, refer to the SmPC.

Call for reporting

Healthcare professionals should report any suspected adverse reactions associated with use of HES solutions for infusion in accordance with the national requirements via the national spontaneous reporting system <detailed information of national spontaneous reporting system>.

It is reminded that these products are subject to additional monitoring due to the above mentioned safety concerns.

Company contact point

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

Communication Plan for Direct Healthcare Professional Communication

DHPC COMMUNICATION PLAN	
Medicinal products	Hydroxyethyl starch (HES) solutions for infusion For a full list of invented names in each Member State, please refer to Annex I
Marketing authorisation holder(s)	For a full list of marketing authorisation holders, please refer to Annex I. 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	Hydroxyethyl starch (HES) solutions for infusion: new measures to reinforce existing restrictions due to increased risk of renal dysfunction and mortality in critically ill or septic patients
DHPC recipients	Anaesthesiologists, intensive care physicians, (chief) hospital pharmacists, emergency care units, further recipients possibly including specialists in infectious diseases, nephrologists, specialists in burn care, specialists in trauma care, nurses, professional societies and national associations to be agreed at national level.
Member States where the DHPC will be distributed	All EU Member States where Hydroxyethyl starch (HES) solutions for infusion are authorised (please refer to annex I)

Timetable	Date
DHPC and communication plan (in English) agreed by CMDh	27 June 2018
Submission of translated DHPCs to the national competent authorities for review	Within 7 calendar days from EC Decision

Timetable	Date
Agreement of translations by national competent authorities	Within 14 calendar days from EC Decision
Dissemination of DHPC	Within 7 working days from agreement of translations by national competent authorities.