

## DUS to Investigate the Routine Use of Hydroxyethyl Starch-containing Infusion Solutions

FK Study Identifier: HE06-027-CNI

### Observational Plan (“Study Protocol”) for Drug Utilisation Study for Hydroxyethyl Starch (HES) Solutions

#### Post-Authorisation Safety Study (PASS) Information

<b>Title</b>	Retrospective, Multinational, Drug Utilisation Study (DUS) to Investigate the Routine Use of Hydroxyethyl Starch (HES)-containing Infusion Solutions in HES-Accredited European (EU) Hospitals after Implementation of a Set of Risk Minimisation Measures
<b>Study Identifier</b>	HE06-027-CNI
<b>Observational Plan Version Identifier</b>	Final 4.0
<b>Date of Last Version of Observational Plan</b>	07 Oct 2020
<b>Included Amendments</b>	Non-substantial amendment 1 (v2.0; 09 Sep 2019), Substantial amendment 1 (v3.0; 03 Jun 2020 and v4.0; 07 Oct 2020)
<b>EU PAS Register Number</b>	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP): EUPAS32145
<b>Active Substances</b>	<u>ATC Code:</u> Blood substitutes and plasma protein fractions B05AA07 hydroxyethyl starch  <u>Active pharmaceutical ingredients:</u> HES 130/0.4 HES 130/0.42
<b>Medicinal Products</b>	<u>Fresenius Kabi Deutschland GmbH:</u> HES 130/0.4-containing products registered in the European countries in which the DUS will be conducted.  <u>B. Braun Melsungen AG:</u> HES 130/0.42-containing products registered in the European countries in which the DUS will be conducted.
<b>Product Reference</b>	Not applicable
<b>Procedure Numbers</b>	<u>Fresenius Kabi Deutschland GmbH:</u> EMA/H/N/PSP/J/0067.1  <u>B. Braun Melsungen AG:</u> Same number as for Fresenius Kabi due to joint procedure

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<b>Marketing Authorisation Holders (MAH) / Study Sponsor</b>	<p><u>Marketing Authorisation Holders:</u> Fresenius Kabi Deutschland GmbH Else-Kröner-Straße 1 61352 Bad Homburg v.d.H., Germany</p> <p>B. Braun Melsungen AG Carl-Braun-Straße 1 34212 Melsungen, Germany</p> <p><u>Study Sponsor:</u> Fresenius Kabi Deutschland GmbH Else-Kröner-Straße 1 61352 Bad Homburg v.d.H., Germany</p>
<b>Joint PASS</b>	Yes
<b>Research Question and Objectives</b>	The primary objective of the imposed DUS is to assess the non-adherence of physicians in HES-accredited hospitals to the approved European Product Information [regarding indication for use, contraindications and posology (dosage)] for HES 130-containing medicinal products in clinical routine after implementation of a set of risk minimisation measures. This allows to evaluate the effectiveness of these measures.
<b>Countries of Study</b>	<p>It is intended to conduct the study in a representative sample of European Union member states like Belgium, Czech Republic, France, Germany, Hungary, Italy, Poland, Spain, The Netherlands, etc.</p> <p>Final country selection will be based on the feasibility survey, non-adherence rates of the first HES DUSs (ENCePP Register No.: EUPAS10897, EUPAS12540), HES 130 sales figures and the willingness of HES-accredited hospitals to participate in this DUS.</p>
<b>Author</b>	<p>Dr. Masood Siddique, Senior Manager Medical Writing</p> <p>Business Unit Parenteral Nutrition, Keto-Analogues and Standard I.V. Fluids Medical, Clinical &amp; Regulatory Affairs Fresenius Kabi Deutschland GmbH Else-Kröner-Straße 1 61352 Bad Homburg v.d.H., Germany</p>

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### Marketing Authorisation Holders

<b>Marketing Authorisation Holders</b>	<b>Fresenius Kabi Deutschland GmbH</b> Else-Kröner-Straße 1 61352 Bad Homburg v.d.H., Germany  <b>B. Braun Melsungen AG</b> Carl-Braun-Straße 1 34212 Melsungen, Germany
<b>MAHs Contact Persons / Sponsor Contact Person</b>	<u>Regulatory Contact:</u> Astrid Schaefer Director, Regulatory Affairs Colloids Medical, Clinical & Regulatory Affairs Business Unit Parenteral Nutrition, Keto-Analogues & Standard I.V. Fluids Fresenius Kabi Deutschland GmbH Else-Kröner-Straße 1 61352 Bad Homburg v.d.H., Germany E-Mail: Astrid.Schaefer@fresenius-kabi.com  Eva Labeirie Team Leader GRA Operations PVR and Medical Device B. Braun Medical AG HC-RA-CH01 9 route de Sorge 1023 Crissier, Switzerland E-Mail: eva.labeirie@bbraun.com  <u>Sponsor Contact Person:</u> Prof. Dr. Martin Westphal Executive Vice President Medical, Clinical & Regulatory Affairs Business Unit Parenteral Nutrition, Keto-Analogues & Standard I.V. Fluids Fresenius Kabi Deutschland GmbH Else-Kröner-Straße 1 61352 Bad Homburg v.d.H., Germany Chief Medical Officer – Fresenius Kabi AG

## **Abstract**

### **Title**

Retrospective, Multinational, Drug Utilisation Study (DUS) to Investigate the Routine Use of Hydroxyethyl Starch (HES)-containing Infusion Solutions in HES-Accredited European (EU) Hospitals after Implementation of a Set of Risk Minimisation Measures

### **Observational Plan Version**

Final 4.0

### **Date of the Observational Plan**

07 Oct 2020

### **Main Author**

Dr. Masood Siddique

### **Rationale and Background**

The concerned Marketing Authorisation Holders (MAHs) have been requested by the European Medicines Agency (EMA) to implement a set of risk minimisation measures as outcome of a regulatory procedure for HES solutions (European Commission decision dated 17 Jul. 2018). This includes for instance implementation of a Controlled Access Programme to ensure that HES solutions are only delivered to accredited hospitals where healthcare professionals expected to prescribe/administer these medicinal products have been trained on their appropriate use.

Since the MAHs of HES solutions shall perform a DUS to assess the effectiveness of the set of risk minimisation measures, this study will be conducted.

### **Research Question and Objectives**

The primary objective of the DUS is to assess the non-adherence of physicians in HES-accredited hospitals to the approved European Product Information (PI) [regarding indication for use and the contraindications and posology (dosage)] for HES 130 solutions in clinical routine after implementation of a set of risk minimisation measures. This allows to evaluate the effectiveness of these measures.

### **Study Design**

Retrospective, non-interventional, multinational, European DUS

### **Population**

Patients treated with HES 130 solutions of the concerned MAHs in HES-accredited hospitals after implementation of a set of risk minimisation measures.

## **Variables**

### Primary Variable:

To assess the non-adherence of hospital physicians to the approved European PIs of HES 130 solutions, the primary variable will be the number and proportion of patients whose treatment during the hospital stay did not adhere to the approved European PIs regarding indication, contraindications and dosage (posology).

### Variables to be Documented:

- Hospital information including date of initial hospital accreditation, type of hospital, pseudonymised unique patient identifier, patient's hospital admission and discharge date, demographics, prehospital field (before admission to the study hospital: crystalloid used, HES 130 used)
- Indication for HES use at start time of first HES infusion within a prescription, contraindications at start time of HES infusion within a prescription, crystalloid use prior to first HES 130 prescription and/or concomitantly, trade name of any prescribed HES 130 product, hospital ward in which the HES 130-prescribing physician was employed, dosage (posology), main medical procedure the patient underwent

## **Data Sources**

Data will be collected retrospectively from charts of patients treated previously with HES 130. All data will be pseudonymised.

## **Study Size**

The sample size calculation is based on the primary statistical unit of the study: Patients treated with HES 130. For potential non-adherence rates of 5 % to 95 % and aiming for a precision (defined as the confidence interval width) of up to 5 percent points of the exact two-sided 95% confidence interval (according to Clopper-Pearson) for the evaluation of non-adherence, a sample size of 1574 patients is required. To compensate for potential inconclusive cases regarding indication or missing data regarding posology (assumption of 10 %), 1749 patients will be documented.

In case the intended targeted sample size of 1749 could not be reached in the documentation period, analysis with a sample size of 1220 (including 10 % compensation for inconclusive regarding indication or missing data regarding posology) will be performed to ensure a precision (confidence interval width) of at least 6 percent points.

However, the sponsor will make any effort to reach the intended target sample size of 1749.

**Data Analysis**

Due to the exploratory character of this study only descriptive statistics will be used for the analysis of the variables.

To assess the non-adherence of hospital physicians to the approved European PIs of HES 130 solutions, the primary variable will be the number and proportion of patients whose treatment during the hospital stay did not adhere to the approved European PIs regarding indication, contraindications and dosage (posology). The full analysis set will comprise all eligible patients.

Furthermore, analysis of non-adherence will also be conducted for each single HES 130 prescription as statistical unit for assessment as secondary measure.

**Estimated Milestones**

<b>Milestone</b>	<b>Planned Date</b>
Start of data collection <sup>a</sup>	19 Feb 2020 (actual)
End of data collection	31 Oct 2020
Registration in the EU PAS Register	01 Nov 2019 (Reg. No. EUPAS32145)
Final report of study results	26 Feb 2021

<sup>a</sup> Date on which the data extraction from patient charts begins

Within the preceding version (v1.0; June 14, 2019) of the observational plan, the dates for start of data collection and end of data collection had been extrapolated based on the request of the European Commission decision for Hydroxyethyl starch-containing medicinal products of 17 July 2018 to submit the study report within 24 months. These dates were depended on e.g. observational plan approval, implementation period of requested risk minimisation measures, the number of available HES-accredited hospitals, the number of HES 130-treated patients, the number of physicians, CRO selection, eCRF generation, hospital selection, contract negotiations, and physicians' availability.

In the above table, the initially estimated milestone dates for "end of data collection" and "final report of study results" have been modified due to several factors which influenced the study execution. Milestone dates for "start of data collection" and "registration in the EU PAS register" have been replaced by the actual dates.