Final Study Report for Drug Utilisation Study for Hydroxyethyl Starch (HES) Solutions

PASS Information

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
Fresenius Kabi Study Identifier	HE06-027-CNI
Version Identifier of the Final Study Report	Version 2.0
Date of Last Version of the Final Study Report	06 Jul 2021
EU PAS Register Number	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP): EUPAS32145
Active Substance	Anatomic Therapeutic Chemical Classification Code: Blood substitutes and plasma protein fractions B05AA07 hydroxyethyl starch Active Pharmaceutical Ingredients: HES 130/0.4 HES 130/0.42
Medicinal Product	Fresenius Kabi Deutschland GmbH: HES 130/0.4-containing products registered in the European countries in which the DUS was conducted. B. Braun Melsungen AG: HES 130/0.42-containing products registered in the European countries in which the DUS was conducted.
Product Reference	Not applicable
Procedure Number	Fresenius Kabi Deutschland GmbH: EMEA/H/N/PSP/J/0067.1 B. Braun Melsungen AG: Same number as for Fresenius Kabi due to joint procedure

Marketing Authorisation Holders	Marketing Authorisation Holders: Fresenius Kabi Deutschland GmbH Else-Kröner-Straße 1 61352 Bad Homburg v.d.H., Germany B. Braun Melsungen AG Carl-Braun-Straße 1 34212 Melsungen, Germany Study Sponsor: Fresenius Kabi Deutschland GmbH Else-Kröner-Straße 1 61352 Bad Homburg v.d.H., Germany
Joint PASS	Yes
Research Question and Objectives	The primary objective of the imposed DUS was 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 allowed evaluation of the effectiveness of these measures.
Countries of Study	This study was conducted in a representative sample of European Union member states, including Belgium, the Czech Republic, France, Germany, Hungary, Italy, Poland, Spain and the Netherlands.
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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

Keywords
Drug Utilisation Study (DUS); Hydroxyethyl starch; Non-adherence; Europe

Rationale and Background
Two drug utilisation studies (DUSs) for hydroxyethyl starch (HES)-containing products were completed in 2017 and suggested that the European Product Information (PI) for these products was not sufficiently adhered to as reflected by non-adherence rates of 77.48 % and 68.8 % of patients.

Further risk minimisation measures (RMMs) were imposed as outcome of the Article 107i procedure (EMEA/H/A-107i/1457) in 2018, one of which was a controlled access programme (CAP). Since implementation, healthcare professionals (HCPs) need to pass a training on the European PI, and HES-containing products are only delivered to accredited hospitals. The current DUS was performed to assess the effectiveness of these measures.

Research Question and Objectives
Assessment of non-adherence of physicians/HCPs to the approved European PI for HES 130-containing medicinal products in clinical routine after implementation of RMMs.

Study Design
Retrospective, non-interventional, multinational, joint European DUS of concerned Marketing Authorisation Holders (MAHs).

Setting
HES-accredited hospitals in Europe.

Subjects and Study Size, Including Dropouts
Eligible subjects received any of the marketed HES130-containing products in the treatment period of May 2019 to September 2020. A sample size of 1749 patients was planned, including a 10 % drop-out rate.

Variables and Data Sources
The primary endpoint was the number and proportion of hospitalised patients whose treatment was not in compliance with the approved European PI regarding indication, contraindications and dosage (posology). Non-adherence could be related to only one or more of these PI sections.

Equivalent analysis was also conducted for each single HES 130 prescription.

Data from the documentation period were collected retrospectively from patient charts. All data were pseudonymised.

Results
The final analysis set includes data from 1863 HES prescriptions from 1851 patients in 32 hospitals in nine European countries.

The overall non-adherence rate to indication, contraindications and dosage was 23.91 % [95 % confidence interval (CI): 21.96 % to 25.96 %] and considerably lower than those in the previous HES DUSs.

Therein, the non-adherence rate for indication was 18.85 % (342 patients). Notably, most of these patients (306/342) did not have any concomitant contraindication. In three hospitals, non-adherence was mostly related to HES use in cardiac procedures or in caesarean section. These procedures accounted for more than half of all patients with non-adherence to PI indication without any contraindications.

The non-adherence to contraindications was reported in 6.48 % of patients, including renal impairment (2.11 %), sepsis (0.97 %) and critical illness (3.57 %, with a low contribution of 0.6 % from ICU).

Median HES dosage administered was 500 mL and non-adherence to dosage was very low (0.16 %). No treatment exceeded 24 h.

Discussion
The current DUS suggests that HES 130-containing products in clinical routine practice are largely used in accordance with the approved European PI.

A considerable improvement compared to 2017 results were the lower non-adherence rates observed in indication and contraindications such as critical illness, renal impairment and sepsis in this DUS.

Overall, the results clearly indicate effectiveness of the new risk minimisation measures.

Marketing Authorisation Holders
Fresenius Kabi Deutschland GmbH
B. Braun Melsungen AG