Abstract of Study Report for the Drug Utilisation Study for Hydroxyethyl Starch (HES) Solutions

PASS information

Title	Retrospective Drug Utilisation Study to investigate the routine use of Hydroxyethyl Starch (HES)-containing Infusion Solutions in Hospitals
Fresenius Kabi Study Identifier	HE06-022-CNI
Version Identifier of the Final Study Report	Version 1.0
Date of Last Version of the Final Study Report	03 July 2017
EU PAS Register Number(s)	ENCePP/SDPP/10897 Date of registration: 07 September 2015
Active Substance	**Fresenius Kabi Deutschland GmbH:** Poly(O-2-hydroxyethyl)starch Sodium chloride Sodium acetate trihydrate (for Volulyte) Potassium chloride (for Volulyte) Magnesium chloride hexahydrate (for Volulyte) **ATC code:** Blood substitutes and plasma protein fractions B05AA07 hydroxyethylstarch
Medicinal Product	**Fresenius Kabi:** The registered product name for the individual products concerned in the European countries in which the Drug Utilisation Study (DUS) was conducted is provided in Annex 1-Number 10 to the main part of the study report
Product Reference	Not applicable
Procedure Number	EMEA/H/N/PSP/0014.2

Abstract of Study Report for the Drug Utilisation Study for Hydroxyethyl Starch (HES) Solutions
Fresenius Kabi Study Identifier HE06-022-CNI

Marketing Authorisation Holder(s)	**Fresenius Kabi Deutschland GmbH** Else-Kröner-Strasse 1 61352 Bad Homburg v.d.H. Germany Note: The registered marketing authorisation holder (MAH) for the individual products in the European countries in which the DUS was conducted is provided in Annex 1-Number 10 to the main part of the study report
Joint PASS	No
Research Question and Objectives	The Pharmacovigilance Risk Assessment Committee (PRAC) requested in October 2013 that HES-solutions must no longer be used to treat patients with sepsis or burn injuries or critically ill patients because of an increased risk of kidney injury and mortality in these patients. However, the benefit-risk balance for HES-containing medicinal products remains favourable in the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient. The objective of the DUS was to assess the adherence of hospital physicians to the revised European Product Information (PI) [Summary of Product Characteristics (SmPC); Package Leaflet] for HES-containing medicinal products concerning indication, posology (dosage) and contraindications (as listed in Annex III of the European Commission decision, dated 19 December 2013).
Countries of Study	Austria, Belgium, the Czech Republic, France, Germany, Hungary, Poland, Spain, The Netherlands
Author	Main authors: [redacted] Medical writing and biostatistics provided by: [redacted]

Marketing Authorisation Holder(s)

Marketing Authorisation Holder(s)	**Fresenius Kabi Deutschland GmbH** Else-Kröner-Strasse 1 61352 Bad Homburg v.d.H., Germany
MAH Contact Person	[redacted]

Abstract

Title

Retrospective Drug Utilisation Study to investigate the routine use of Hydroxyethyl Starch (HES)-containing Infusion Solutions in Hospitals

Keywords

Drug Utilisation Study (DUS), hydroxyethyl starch (HES) solutions, patient charts, non-adherence, revised European Product Information

Rationale and Background

Following the Pharmacovigilance Risk Assessment Procedure according to Article 107i of Directive 2001/83/EC for HES-containing medicinal products (EMEA/H/A-107i/1376), which was finalised by the European Commission decision on 19 December 2013, revisions of the European Product Information (PI) [Summary of Product Characteristics (SmPC); Package Leaflet] had to be implemented for risk minimisation. For example, the indication had to be revised to "treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient" and new contraindications as well as new special warnings and precautions for use had to be implemented.

In addition, a "Direct Healthcare Professional Communication" (DHPC) had to be disseminated in November 2013 in all European Union (EU) member states in order to inform the Healthcare Professionals about the new PI revisions including a summary of the new recommendations for the restricted use of HES-containing medicinal products and the reasons for this.

Furthermore, a variation to revise the PI was approved in May 2014. Subsequently, the revised PI had to be implemented in all EU member states by November 2014.

To evaluate the effectiveness of these risk minimisation measures, Fresenius Kabi was requested by the European Medicines Agency (EMA) as an outcome of the Article 107i procedure (EMEA/H/A-107i/1376) in 2013 to also conduct a Drug Utilization Study (DUS) with HES-containing medicinal products in several EU member states.

Research Question and Objectives

The objective of the DUS has been to assess the adherence of hospital physicians to the revised European PI for HES-containing medicinal products concerning indication, posology (dosage), and contraindications (as listed in Annex III of the European Commission decision for HES-containing medicinal products dated 19 December 2013).

Study Design

The study was designed to be a retrospective, anonymised, non-interventional and multinational European DUS according to EMA's Pharmacovigilance Risk Assessment Committee (PRAC) request.

Setting

The DUS was conducted at 45 sites in nine European countries (Austria, Belgium, the Czech Republic, France, Germany, Hungary, Poland, Spain, and The Netherlands), covering the documentation period from 01 January 2015 to 01 May 2015.

Patients and Study Size, Including Dropouts

At least 3000 patients were required to be documented in order to achieve sufficient precise estimates per country and for the overall population. Finally, the full analysis set (FAS) consisted of 3890 patients ranging from 111 in Spain to 733 in France.

Variables and Data Sources

Data collection comprised chart data of patients treated with HES-containing medicinal products of Fresenius Kabi (in the following also referred to as "HES" or "HES product(s)"). Requested factors determining adherence or non-adherence to the revised SmPC included duration of HES treatment, daily dose of HES administration, co-morbidities, age, indication for HES treatment, and specialty of hospital ward.

Results

Data on the use of Fresenius Kabi's HES products within the predefined timeframe were collected between 18 May 2016 and 12 October 2016.
Most patients were ≥18 years of age (69 were <18 years old). The most common documented main diagnoses [International Classification of Disease, tenth revision (ICD-10) Chapter] at hospital admission were neoplasms (19.69 % of patients), followed by diseases of the circulatory system (16.40 %), diseases of the musculoskeletal system and connective tissue (14.63 %), injury, poisoning and certain other consequences of external causes (13.88 %), pregnancy, childbirth and the puerperium (10.46 %), and diseases of the digestive system (10.03 %).

The overall rate of non-adherence to the SmPC was determined to be 77.48 % (95 % confidence interval [CI]: 76.13 %, 78.79 %). Non-adherence rates differed across the nine countries ranging from 61.37 % (95 % CI: 56.93 %, 65.67 %) in the Czech Republic to 89.74 % (95 % CI: 86.30 %, 92.57 %) in Belgium. No overall assessment of non-adherence could be made for 1.11 % of patients due to missing data.

Adherence to the revised maximum daily dose of 30 mL/kg body weight for 6 % HES solutions and the duration of 24 hours of treatment was up to 99.25 % and up to 96.97 %, respectively.

The retrospective, anonymised design of this study did not allow for the appropriate evaluation of the effectiveness of the imposed risk minimisation measures. The investigators had limited information available in the patient charts, and the results could not be further verified due to the limitations of the study design. Therefore a meaningful and reliable interpretation of the non-adherence rate is not possible.

The most common criteria determining non-adherence were treatment of hypovolaemia due to other indications than "treatment of hypovolaemia due to acute blood loss" (62.67 % of patients) and treatment despite presence of contraindications (presence of relevant co-morbidities in 34.16 % of patients).

The most commonly documented co-morbidities were disturbed fluid status (dehydration or hyperhydration, 16.76 %), congestive heart failure (9.07 %), and renal impairment (8.07 %).

At least one adverse event (AE) was documented in 238 patients (6.12 %). Serious adverse events (SAEs) were recorded in 193 patients (4.96 %) and SAEs with fatal outcome were reported in 44 patients (1.13 %). One patient had a fatal SAE (cardiac arrest), according to the investigator's judgment with a reasonable possibility that the SAE was associated with HES administration. A more detailed medical analysis of the AEs was not possible due to the anonymised, retrospective data collection from patient charts.

Discussion

The Marketing Authorisation Holder (MAH) concludes that the design of the study did not allow for the appropriate evaluation of the effectiveness of the imposed risk minimisation measures. Data was difficult to interpret within the specific criteria of the study design. In several cases the indication for HES use may have been incorrectly documented as "treatment of hypovolaemia without acute blood loss", leaving investigators to rely on limited information in the patient charts. For instance, "treatment of hypovolaemia with/without acute blood loss" has no unique allocated ICD-10 code, thus not allowing a clear classification of the medical term.

For example, it is likely that in some cases physicians only documented extraordinary and unexpected blood loss. "Acute" blood loss might have been understood as "severe" bleeding but not as "expected procedure-related" bleeding. The data available contributed to a misinterpretation of the calculated rate of non-adherence.
Cross-validation of blood loss by haemoglobin/haematocrit and blood transfusions was not possible because these values were not intended to be documented at baseline nor at later stages according to the study protocol.

Likewise, cross validation of renal function was not possible as creatinine/urea concentrations were not intended to be collected.
As confirmed by external experts, this is not in line with clinical practice, because blood loss is always cross-checked with changes of haemoglobin or haematocrit values. Similarly, renal function is typically judged by changes in creatinine/urea nitrogen values and urine output. The absence of such plausibility checks does not allow for accurate medical assessment of the collected data, and weakens the overall analysis of the results to an extent that reliable conclusions cannot be drawn.

The contraindication "dehydration" might not have been adequately assessed as hypovolaemia and dehydration are difficult to differentiate without examining the patients. In clinical practice, it is impossible to define dehydration by using the patients' charts alone. "Hypovolaemia" represents part of the indication for use, whereas "dehydration" represents a lack of water and is a contraindication.
According to the data entry, in one EU-country the percentage of patients with dehydration as relevant co-morbidity before HES-administration amounted to almost 40 % (249 of 637 patients with dehydration in total) which is higher as compared to all other countries and does not reflect the standard clinical routine. As a consequence, it is probable that many physicians were confused by the terminology of the study protocol.

A further aspect refers to the contraindication "Congestive heart failure", which are patients of the NYHA (New York Heart Association) classification III and IV. Out of 353 patients with congestive heart failure, 84 were classified as NYHA stage I and 134 as NYHA stage II. Patients graded as NYHA stage I or II were incorrectly interpreted as congestive heart failure, although these grades do not represent contraindications in the SmPC. However, these patients also contributed to the non-adherence rate.

The analyses of the documented AEs have not revealed any safety signal. This is confirmed by a review of Fresenius Kabi's pharmacovigilance database. In particular, during the period from beginning of 2012 until end of 2016, a constant rate of about 12 spontaneous reports per year has been obtained from the European member states. Hence, there is no association of the number of the reported cases to the observed non-adherence rate.

In summary, due to the limitations of the retrospective, anonymised design and the data available for analysis, the study provided a highly questionable rate of calculated non-adherence which does not allow reliable conclusions.

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