10 February 2022
EMA/596511/2022
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC non-interventional imposed PASS final study report assessment report

Active substance: hydroxyethyl starch

Procedure no.: EMEA/H/N/PSR/J/0031

Note

Assessment report as adopted by the PRAC and considered by the CMDh with all information of a commercially confidential nature deleted.

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List of abbreviations

AG	Aktiengesellschaft (Incorporation)
CI	Confidence Interval
CAP	Controlled Access Program
CRO	Contract Research Organisation
DUS	Drug Utilisation Study
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ESAIC	European Society of Anaesthesiology and Intensive Care
EU	European Union
EU PAS Register	European Union Electronic Register of Post-authorisation Studies
FAS	Full Analysis Set
GmbH	Gesellschaft mit Beschränkter Haftung (Limited Liability Company)
HCP	Healthcare Professional
HES	Hydroxyethyl Starch
IEC	Independent Ethics Committee
kg	Kilogram
MAH	Marketing Authorisation Holder
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mL	Millilitres
mL/kg	Millilitres per kilogram
PDMS	Patient Data Management System
PI	Product Information

PRAC	Pharmacovigilance Risk Assessment Committee
PSSV	Pre-study Site Visit
PT	Preferred Term
RRT	Renal Replacement Therapy
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Systems
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedures
TFLs	Tables, Figures and Listings

1. Background information on the procedure

In order to fulfil the obligation to submit the results of an imposed non-interventional PASS in accordance with Article 107p of Directive 2001/83/EC, the Marketing Authorisation Holder (MAH) Fresenius Kabi Deutschland GmbH submitted, also on behalf of B. Braun Melsungen AG on 24 February 2021, their joint PASS final report to the European Medicines Agency (EMA) for Poly(O-2-hydroxyethyl) starch (HES or hydroxyethyl starch) solutions for infusion.

For an overview of the nationally authorised products covered in the context of this final study report, please see Appendix I of the Pharmacovigilance Risk Assessment Committee (PRAC) recommendation.

HES solutions for infusion are authorised for managing of hypovolaemia due to acute blood loss only when crystalloids alone are not considered sufficient. This restricted indication of HES solutions for infusion, previously authorised for the treatment and prophylaxis of hypovolaemia associated with various conditions, was part of the PRAC recommendation for risk minimization measures (RMMs) following reviews in 2012 and 2013 of the benefits and risks of HES solutions for infusion, within Article 31 (EMEA/H/A-31/1348)[1] and 107i referral (EMEA/H/A-107i/1376)[2] procedures. These reviews were triggered by the results from large randomised clinical studies which showed an increased risk of mortality in patients with sepsis and an increased risk of kidney injury requiring dialysis in critically ill patients who received HES solutions for infusion.

In addition, the product information was updated with new contraindications and revised warnings. The full list of contraindications includes sepsis, critically ill patients (typically admitted to the intensive care unit), 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, but also hypersensitivity to the product, severe hypernatraemia or severe hyperchloraemia, severe hyperkalaemia (for HES containing potassium chloride), congestive heart failure, organ transplant patients.

The PRAC also recommended that two phase IV randomised clinical trials (TETHYS and PHOENICS) with an appropriate control and clinically meaningful endpoints are conducted, respectively in trauma and elective surgery to provide more evidence on the efficacy and safety (studies still ongoing). In 2013, the PRAC also recommended that a European Drug Utilization Study (DUS) is conducted to evaluate the effectiveness of the recommended RMMs. Two separate DUSs were conducted by two MAHs, one by Fresenius Kabi Deutschland GmbH and one by B. Braun Melsungen AG. All of these are imposed studies (category 1 PASS), thus being conditions to the marketing authorisations.

Results from DUSs which became available in 2017 (assessed in EMEA/H/A-107i/1457)

Results from the two first DUSs were assessed in 2017 within an Article 107i review (EMEA/H/A-107i/1457[3]). Both studies showed that the recommended restrictions for use were not sufficiently adhered to, especially because HES solutions for infusion continued to be used in critically ill patients and patients with sepsis, despite contraindications introduced in 2013 due to the risk of kidney injury and death in these patient groups.

In July 2018, this review was finalised and the European Commission decided that HES solutions for infusion should remain on the market provided that a combination of additional RMMs was implemented to ensure that HES solutions for infusions are not used in patients at risk of serious harm. New RMMs included a controlled access programme (CAP), warnings in the product information and a

[1] Hydroxyethyl starch Article 31 referral (2013) – PRAC assessement report (europa.eu)
[2] Hydroxyethyl starch Article 107i referral (2013) – PRAC assesssment report (europa.eu)
[3] Hydroxyethyl starch containing medicinal products – Article 107i referral (2018) | European Medicines Agency (europa.eu)

communication to HCPs (Direct healthcare professional communication, DHPC). The MAHs were also requested to conduct another DUS (additional pharmacovigilance activity) on the effectiveness of these new RMMs to ensure HES solutions for infusion are only used according to the terms of the marketing authorisation of these medicinal products. The CAP, which was imposed as a condition to the marketing authorisation, was aimed to ensure that HES solutions for infusion are only delivered to accredited hospitals / centres where HCPs expected to prescribe / administer these medicinal products have been trained on their appropriate use.

Since adherence to the newly implemented routine and additional RMMs is critical to ensure a positive benefit-risk balance of the HES products, the further DUS to assess the effectiveness of these new RMMs was imposed as a condition to the marketing authorization (category 1 PASS). The protocol of this DUS has been reviewed and agreed by the PRAC within a previous procedure[4].

[4] PRAC minutes of 11-14 June 2019 (europa.eu)

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
Version identifier of the final study report	Version 2.0
Date of last version of the final study report	26 April 2021
EU PAS register number	ENCePP: EUPAS32145
Active substance	ATC Code: Blood substitutes and plasma protein fractions B05AA07 hydroxyethyl starch Active Pharmaceutical Ingredients: HES 130/0.4 HES 130/0.42
Medicinal product	Hydroxyethyl starch-containing solutions for infusion
Product reference	Not applicable
Procedure number	EMEA/H/N/PSR/J/0031
Marketing authorisation holder(s)	Fresenius Kabi Deutschland GmbH, B. Braun Melsungen AG
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.
Country(-ies) of study	Belgium, the Czech Republic, France, Germany, Hungary, Italy, Poland, Spain, the Netherlands.

2. Scientific conclusions and actions

Drug utilization study (DUS) EUPAS32145

The DUS assessed the effectiveness of the new set of RMMs as implemented after the referral procedure EMEA/H/A-107i/1457 in 2018. These included, in addition to the already previously agreed RMMs, a CAP where healthcare professionals (HCPs) need to pass a training on the approved product information, and HES-containing products only to be delivered to accredited hospitals. The protocol of the DUS has been reviewed and agreed by the PRAC within a previous procedure[4]. Overall, the design was considered appropriate to evaluate adherence to the agreed RMMs.

Study design

The study was a retrospective, non-interventional, multinational, European DUS sponsored by the two MAHs Fresenius Kabi Deutschland GmbH, and B. Braun Melsungen AG jointly. It was undertaken among certain hospitals accredited for the use of HES 130 solutions for infusion within nine European Union (EU) Member States namely Belgium, the Czech Republic, France, Germany, Hungary, Italy, Poland, Spain and the Netherlands.

Eligible subjects received any of the marketed HES 130-containing products in the treatment period from May 2019 to September 2020. The DUS recruited 1851 patients fulfilling the study eligibility criteria for 1863 prescriptions in 32 accredited sites/hospitals. It was possible to assess relevant parameters in relation to adherence / non-adherence for 97% of prescriptions. Data from the documentation period were collected retrospectively from patient charts. All data were pseudonymised.

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

Main results

Overall, the rate of non-adherent prescriptions (indication, contraindication, and/or posology) of HES solutions for infusion was 23.91% (95% confidence interval [CI] 21.96 - 25.96). This corresponded to 18.85% of non-adherence to the indication, 6.55% for contraindications, and 0.16% for posology.

A subgroup analysis by countries showed that the proportions of prescriptions with an overall conclusion of non-adherence to the product information ranged from 5.7 % (95 % CI: 4.0 % to 7.7 %) in Germany to 94.1 % (95 % CI: 88.3 % to 97.6 %) in Belgium. The PRAC noted that non-adherence to the product information was particularly high in four Member States – Belgium, the Netherlands, Italy and France, ranging from 81.6 % to 94.1 % in Belgium, the Netherlands and Italy and 39.9% in France. The degree of non-adherence in the nine Member States is reported in the table below.

	Sites (N= 32)	Patients (N=1851)	HES 130 Prescriptions (N=1863) n (%) of all prescriptions	% of non-adherence (95 % CI)
Germany	10	657	660 (35.4%)	5.7 % (4.0 % - 7.7 %)
France	6	300	305 (16.4%)	39.9% (34.2 % - 45.9 %)
Spain	3	255	255 (13.7%)	<20%
Czech Rep	4	223	224 (12.0%)	<20%
Hungary	3	121	121 (6.5%)	< 20%

Belgium	2	119	119 (6.4%)	94.1 % (88.3 % - 97.6 %)
Poland	1	81	81 (4.3%)	25.9 % (16.8 % - 36.9 %)
The Netherlands	1	60	60 (3.2%)	85.0 % (73.4 % - 92.9 %)
Italy	2	35	38 (2.0%)	81.6 % (65.7 % - 92.3 %)

- Non-adherence to the indication

Non-adherence to the indication constituted 18.85% of all non-adherent prescriptions.

The most frequent prescriptions with non-adherence to the indication were observed in 2 sites (2/2) in Belgium (n=60, 100% and n=51, 86.4% of all prescriptions), followed by one site (1/1) in The Netherlands (n=51 prescriptions, 85.0%). Non-adherence to the indication in 6 sites in France ranged from 12.1 to 79.5% of prescriptions and in 2 sites in Italy from 57.1 to 100% of prescriptions.

In Belgium, the reasons for non-adherence to the indication in one of two sites were anaesthetic complication (vascular) for all 60 prescriptions. For the second site, Caesarean section was recorded as the reason for non-adherence in n=42 (71.2%) prescriptions.

In the Netherlands, HES solutions for infusions were most often used in cardiac operation and for extracorporeal circulation (n=44 prescriptions, 73.3%).

In a field analysis by the MAHs, one site in Belgium (1/2) confirmed off-label use to be attributed to a standard treatment protocol at the institution and five interviewed Belgian sites confirm use of HES solutions for infusion to prevent hypotension in patients during Caesarean section with spinal anaesthesia. Two interviewed sites in The Netherlands confirmed that they were using HES solutions for infusion in cardiac surgery.

- Non-adherence to the contraindications

The breakdown of non-adherence to contraindications is presented in the table below:

	Breakdown per contraindication
Total	122 (6.55%)
Critical Illness	66 (3.54%)
Renal Impairment	41 (2.20%)
Sepsis	18 (0.97%)

The most frequent non-adherence to contraindications was observed in 2 sites in Italy (n=17, 100% and n=12, 57.1%, prescriptions of those recorded in these two sites), followed by 1 site each in France (n=15, 26.3%) and in Spain (n=13, 23.6%).

The 18 patients (0.97%) with sepsis, who were treated with HES solutions for infusion came from 10 sites in 6 countries. Seven (7) patients had in addition to sepsis one more contraindication (renal impairement (3), severe coagulopathy (3), severe impaired hepatic function (2), renal replacement therapy (1), and dehydratation (1)).

- Non-adherence to the posology

Non-adherence to posology was low (0.16 %), median dose was 500 mL and median maximum duration was 0.583 h (range: 0.02 h to 23.97 h).

Following review of the results from this DUS, a number of questions were raised to the MAHs, both regarding study details, generalisabilty and representativeness as well as concerns raised regarding continued non-adherence to important measures to avoid use of HES solutions for infusion in patients at risk for serious harms.

The PRAC's discussion on the DUS results

The representativeness of the DUS results for the EU countries was thoroughly discussed by the PRAC. Thirty-two accredited hospitals in nine countries contributed patients to the DUS, which represents a widespread EU distribution.

Representativeness of results was also analysed by a post-hoc sensitivity analysis where the site which contributed the largest number of patients (149 patients out of a total of 1851) was excluded. No relevant effect of this specific site was identified on overall results, further supporting general representativeness of the results.

Overall, the DUS is considered to be representative of the main clinical usage in the EU and key results are reliable. The PRAC noted that there may be some use of HES solutions for infusion outside a hospital setting (e.g. emergency use in military setting) which was not captured by the DUS. However, this is not considered to question the current data from the DUS, or impact the results of the study.

The PRAC noted that overall non-adherence to the product information remained high (23.91%). The PRAC discussed, in particular, the results of the countries where non-adherence to the product information was very high, namely Belgium, the Netherlands, Italy and France. Although study comparisons of the individual DUSs should be made with caution, the PRAC noted that the non-adherence to contraindications, and indications was more frequent within the current DUS in sites in Belgium and the Netherlands, than in the previous two DUSs assessed in 2017. This points to that the RMMs implemented as a result of the 2018 referral procedure were not adhered to, despite all sites having undergone training for the purposes of accreditation. Thus, non-adherence is likely not due to lack of awareness in Belgium or the Netherlands. Furthermore, the non-adherence to the product information was high in Italy (81.6%) and France (39.9%) and was between 5.7% and 25.9% in other Member States represented in the current DUS. The combination of (additional) RMMs (agreed in 2018) therefore does not effectively ensure that HES solutions for infusion are not used in patients at risk for serious harm.

The PRAC particularly expressed serious concerns regarding a high non-adherence to contraindications, constituting 6.6% of non-adherent prescriptions, of which 3.5% of prescriptions were for critically ill patients, 2.2% of prescriptions for patients with renal impairment and approximately 1% of prescription were attributed to patients with sepsis. Moreover, the results of the current DUS results showed that 7 of 18 patients with sepsis treated with HES solution, had in addition to sepsis one more contraindication (renal impairment, severe coagulopathy, severe impaired hepatic function, renal replacement therapy and dehydration).

With regard to reasons for non-adherence to the indication, the MAHs referred to a field research which showed that in two sites (2/2) in Belgium, the main reason for non-adherence to the indication (in 93.3%) were the use for Caesarean section and anaesthetic complications (vascular). In the Netherlands, cardiac operation and extracorporeal circulation were reasons for 44 (73.3%) non-adherent prescriptions. Considering this further information provided by the MAHs, non-adherence to indication seems to reflect a usual practice in these Member States. Furthermore, available information

for other Member States did not allow to conclude that results observed in sites in France and Italy are representative of the situation at a national level or not. In view of what seems to be deliberate non-adherence to the therapeutic indication by the prescribers, it is seriously questioned if further RMMs may result in decrease of non-adherence among those not following the current restrictions.

As discussed in the last PSUSA procedure (PSUSA/00001694/202103), the patient exposure cannot be precisely determined and is estimated based on the sold units. Although sales of HES solutions for infusion overall decreased by 26% (Fresenius Kabi) and by 13% (BBraun) from 2019 to 2020 in the EEA, these sales data support that there is still exposure to a considerable number of patients since the implementation of the CAP (for BBraun in 2020: 37 310 patient-days, for Fresenius Kabi: 678 684 patients yearly; these figures should be taken with caution due to different method of estimation between MAHs), in particular in view of the overall adherence to a lower posology (i.e. less HES solution for infusion used for each patient). This raises serious concern, considering the high rates of non-adherence to key restrictions such as indication and contraindications, meaning that a significant proportion of patients who are exposed to HES solutions for infusion should not have been exposed in view of the increased risk of developing serious adverse events.

The PRAC noted the general adherence to the recommended dose and duration of treatment. However, the PRAC concluded that it is not possible to identify a cut-off level below which harm is avoided in vulnerable populations, and that evidence demonstrating harm is seen in patient groups treated at doses consistent with the current recommendations. Therefore, it cannot be concluded that the use in contraindicated patients seen in the current DUS is safe because of the dose regimens used. The restricted posology recommendations were implemented in 2013 to enhance safe use of HES solutions for infusions.

These current DUS results showed that among the restriction in use implemented in 2013, some of the restrictions seem to be adhered to, namely the recommendations on dose and duration of treatment. Since adherence to some of the restrictions seems at an acceptable level this suggests that the HCPs are aware of the restrictions and it might be a choice not to adhere to others.

The PRAC acknowledged that 100% adherence to the product information might not be feasible, however the level of non-adherence should be proportionate to the established risks, and at least the indication and contraindications should be well adhered to. Considering that serious harm has been demonstrated in patients with sepsis, renal impairment or critical illness, the significant proportion of use of HES solutions for infusion in these contraindicated populations in combination of high patient exposure raises a significant public health concern.

Based on the above, the PRAC concluded that the RMMs introduced in the previous 2018 referral procedure have not been sufficiently effective, as the assessment of the current DUS results demonstrates that key restrictions of the use of HES solutions for infusion are not sufficiently adhered to in order to mitigate the identified and serious risks associated with HES solutions for infusion.

Additional information provided by the MAHs

In response to requests from the PRAC, the MAHs submitted additional information and arguments. In addition to further details and considerations regarding the DUS results, the MAHs argued that overall use of HES solutions for infusion, as well as non-adherence to the product information had decreased from 2018, when the new RMMs were implemented.

- Post-marketing safety data

The MAHs confirmed that the number of spontaneous individual case safety reports (ICSRs) in EEA countries decreased following the first DHPC in November 2013 after the Article 107i referral, notifying

the HCPs of the established risks and implemented restrictions of use. It was also pointed out that nine ICSRs have been reported in EEA from 2019 to March 2021. None of the cases had a fatal outcome. Off-label use was suggested in most of these cases considering the reported indication, and Caesarean section was mentioned in 3 cases. The ADRs were mainly serious but confounding factors (co-suspect drugs, underlying diseases) or alternative explanations were noticed in all cases.

The PRAC noted the current post-marketing data available for HES solutions for infusion where only few ICSRs have been reported after the implementation of the most recent RMMs in 2018. However, given the nature of these products, and the fact that they have been on the market for decades, a considerable level of underreporting of ADRs may be expected. In particular, these products are used in complex or emergency situations in which a patient is receiving multiple therapies; it is therefore difficult to identify a possible causative agent for any adverse drug reaction experienced which may further impact the level of reporting. The potential for a time delay between an acute exposure to HES solutions for infusion, and occurrence of renal impairment or death may also make it less likely for HES solutions for infusion to be identified as a possible causative agent, further contributing to underreporting. Furthermore, the risk of increased mortality and renal failure have been established and confirmed based on data from clinical studies and not spontaneous reporting. The few ISCRs received during 2019 – 2021 do not provide sufficient reassurance regarding lack of serious concerns from the non-adherence reported in the DUS.

The MAHs also pointed out that this is in line with the data from the latest PSUSA (PSUSA/00001694/202103), for which no new important identified risks have been detected. However, PRAC noted that the risks due to incorrect use of HES are not new, but well defined from clinical studies.

- Additional publications

The MAHs also provided eight recently published studies, including six clinical trials[5] (Gupta 2021, Suzuki 2020, Kwak 2018, Nizar 2020, Mahrous 2021, Lee 2021) and two meta-analyses[6] (Chappel 2021 and Pensier 2021).

The six randomized controlled trials concerned studies where HES solutions for infusion were compared to albumin in four trials, and to crystalloids in two trials. The four trials comparing HES solutions for infusion to albumin (Lee 2021, Suzuki 2020, and Kwak 2018) or Gelaspan (Nizar 2020) concerned patients with major surgery: cardiac, orthopaedic, or abdominal (hepatic and pancreatic) surgeries. These four trials included few patients (a maximum of 66 patients per arm). In three trials (Nizar 2020, Kwak 2018, and Suzuki 2020), HES solutions for infusion were used either to prevent hypotension induced by spinal anesthesia or during surgery depending on the stroke volume variation,

[5] P. Gupta and all: Efficacy of Intravenous Fluid Plasmalyte and 6% Hetastarch in Preventing Spinal Anaesthesia Induced Hypotension in Patients undergoing Lower Abdominal Surgeries: A Randomised Clinical Study. Journal of Clinical and Diagnostic Research. 2021 May, Vol-15(5): UC26-UC30
T. Suzuki and all: Open randomized trial of the effects of 6% hydroxyethyl starch 130/0.4/9 and 5% albumin on safety profile, volume efficacy, and glycocalyx degradation in hepatic and pancreatic surgery. Journal of Anesthesia (2020) 34:912–923
H.J. Kwak and all: Acid/base alterations during major abdominal surgery: 6% hydroxyethyl starch infusion versus 5% albumin Korean Journal of Anesthesiology VOL. 71, NO. 6, December 2018
N. D. Nizar and all: Comparing the Effects of Pre-loading with Gelatine 4% Plasma Volume Expander and 6% Hydroxyethyl Starch Solution Before Spinal Anaesthesia for Lower Limb Orthopaedic Surgery. Malays J Med Sci. 2020;27(6):68–78
S. Mahrous and all: Evaluation of two different fluids regimens on central venous-to-arterial Carbon Dioxide difference (pCO2 gap) - a randomized controlled trial. Egyptian Journal of Anesthesia 2021, VOL. 37, NO. 1, 113–122
M. J. Lee and all: Effect of 6% Hydroxyethyl Starch 130/0.4 on Inflammatory Response and Pulmonary Function in Patients Having Cardiac Surgery: A Randomized Clinical Trial Anesthesia and Analgesia October 2021 • Volume 133 • Number 4
[6] D. Chappell and all: Safety and efficacy of tetrastarches in surgery and trauma: a systematic review and meta-analysis of randomised controlled trials. British Journal of Anaesthesia, 127 (4): 556e568 (2021)
J. Pensier and all : Hydroxyethyl Starch for Fluid Management in Patients Undergoing Major Abdominal Surgery: A Systematic Review With Meta-analysis and Trial Sequential Analysis. Anesthesia and Analgesia 2021

or even systematically after abdominal exploration. In only one study (Lee 2021), HES solutions for infusion were administered in case of arterial pressure decrease/increased heart rate or acute surgical haemorrhage. The two remaining trials (Marhous 2021, Gupta 2021) concerned studies where HES solutions for infusion were compared to crystalloids in patients with major orthopaedic surgery or lower abdominal surgery with spinal anaesthesia. Few patients were included in these studies (about forty patients in each arm). HES solutions for infusion were used to prevent spinal anesthesia or during surgery in case of decrease in mean arterial blood pressure or an increase in heart rate. No post-operative haemorrhage was clearly specified.

Six trials were conducted outside the EU, five in Asian or North African countries, and one study in the USA. In five studies, no significant difference was observed in terms of safety or efficacy between HES and other colloid solutions. Only one study (Gupta 2021) showed that pre-loading with 5 mL/kg of 6% Hetastarch (HES) is more effective than 15 mL/kg of Plasmalyte (crystalloids) in preventing hypotension in patients undergoing lower abdominal surgeries under spinal anaesthesia. In the publication of Marhous et al., the authors concluded that in major orthopedic surgeries, fluid resuscitation using colloids (HES) is associated with more stable hemodynamics and better tissue perfusion compared to crystalloids. Generally, these six small studies were not always conducted in accordance to the terms of the marketing authorisation and did not bring sufficient data that could significantly change the benefit-risk balance of HES solutions for infusion.

The two meta-analyses included patients in adult surgery and trauma. The Pensier's meta-analysis analysed seven prospective randomised trials including 2398 adults during major abdominal surgery with HES vs. crystalloids. The results showed no difference in risk of 30-day acute kidney injury (AKI) between the groups (RR=1.22, 95% CI, 0.94–1.59; P = .13). The Chappell's meta-analysis analysed 90 prospective randomized trials with HES vs. crystalloid, gelatine, or albumin in surgery and trauma. The results showed no differences in renal function and need of renal replacement therapy (RRT) between surgical patients treated with HES versus comparators. Mortality was comparably low with no differences between HES and comparators. The results imply that a combination of crystalloids and HES has clinically beneficial effects over using crystalloids alone when used with adequate indication. However, regarding a subgroup analysis, AKI events were more frequent in the HES group compared to the crystalloids group (RR 1.31; 95% [1.09-1.59] P=0.004). The use of vasopressors drugs was significantly more frequent with crystalloid compared with HES (63.4% versus 51.4%; risk ratio, 0.80; 95% CI, 0.75-0.85; P<0.001).

In Chappell's meta-analysis, the majority of the retained clinical trials comparing HES solutions for infusion with crystalloid solutes were published before the previous referral of 2017 and had thus already been assessed by the PRAC. The four articles published since 2018 comparing HES solutions for infusion with crystalloids did not identify an increased risk of renal toxicity in patients receiving products containing 6% HES.

In conclusion, these data do not provide sufficient evidence to challenge the benefits and risks of HES solutions for infusion as established in previous reviews and do not provide any meaningful information with regards to any potential change to the safety profile of HES solutions for infusion.

Serious harm has been demonstrated in the large randomised clinical trial, when HES solutions for infusion are used in contraindicated populations. In the referral procedures in 2012 and 2013, it has been established that HES, compared to crystalloids shown to be associated with an increased risk of mortality in patients with severe sepsis and adverse renal effects in particular in critically ill patients. In two large randomised clinical trials 6S[7] (Perner A et al. 2012) and VISEP[8] (Brunkhorst FM et al.

[7] Perner A, Haase N, Guttormsen AB et al. Hydroxyethyl starch 130/0.42 versus ringer's acetate in severe sepsis. N Engl J Med 2012;367(2):124-34

2008), treatment with HES in critically ill patients has been associated with increased risk of mortality at day 90 in patients with sepsis and septic shock. These findings were confirmed by two meta-analyses[9] (Zarychanski et al. 2013 ; Perel, P., I. Roberts, and K. Ker, 2013). Results of studies VISEP, 6S trial and CHEST[10] (Myburgh et al. 2012) shown an increased risk of adverse renal effects in patients with sepsis or critical illness treated with HES, including renal failure and a higher risk for renal replacement therapy. Recent publications do not challenge these literature data and previous European assessments.

Discussion on proposed RMMs

The MAHs also proposed further RMMs to address the continued non-adherence to the product information. These included:

- revision of the educational training material content of the CAP,
- mandatory recertification of HCPs on annual basis with a mandatory post-training test of HCPs,
- mandatory accreditation of hospital departments on annual basis,
- enhancement of engagement letter to be signed by the head of the department by all HCPs using HES to confirm that HES-containing products are not used in the absence of acute blood loss (for prophylaxis),
- letter to pharmacist listing the accredited departments that can be supplied with HES-containing products,
- product information amendments.

During the oral explanation held on 7 February 2022, the MAHs proposed an additional measure, namely a mandatory entry by hospitals of information on indication and contraindications on single patient basis into an electronic database in four selected Member States (Belgium, the Netherlands, Italy, France). This information would then be used to restrict delivery only to hospitals with levels of non-adherence under 20%. The MAHs proposed to report on this measure in upcoming PSURs.

The PRAC considered the proposals for further RMMs from the MAHs. Particularly feasibility and effectiveness of the further/additionally proposed RMMs were discussed. Proposals for enhancement of an engagement letter and a letter to pharmacists listing the accredited departments that can be supplied with HES solutions for infusion, were considered by the PRAC as measures with uncertain impact in preventing use outside of the terms of the marketing authorisation, particularly in the context of already existing measures to restrict supply of HES solutions for infusion to accredited sites/hospitals and certified HCPs. The PRAC concluded that because cases of non-adherence to the product information in some countries are not due to lack of awareness of the RMMs implemented in 2013 and 2018, further revision of the educational materials for HCPs, mandatory annual retraining as well as further communication via the means of e.g. a DHPC, would not sufficiently alter existing prescribing behaviours. By adding more complexity, it could even lead to the opposite, namely more non-adherence by HCPs to the product information and implemented measures.

[8] Brunkhorst FM, Engel C, Bloos F et al. Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis. N Engl J Med 2008; 358(2):125-39

[9] Zarychanski, R., et al., Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. JAMA, 2013. 309(7): p. 678-88. Perel, P., I. Roberts, and K. Ker, Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev, 2013. 2: p. CD000567.

[10] Myburgh J, Finder S, Bellomo R et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 2012; 367:1901-11

The PRAC also discussed the latest proposal of mandatory entering of single patient information in a database in four Member States and noticed that no assessment of its feasibility had been presented by the MAH. The PRAC questioned the potential impact of this measure in terms of minimising risk for patients, considering that only retrospective data would be entered in view of the therapeutic indication of HES solutions for infusion (i.e. at acute blood loss). The PRAC also questioned feasibility of this proposal and concluded that it will represent an additional burden to the healthcare system by administrative constraints in a setting where clinical outcome is strongly dependent on the ability to make rapid decisions.

The PRAC also considered other RMMs including changes to the product information and updates of national or European therapeutic guidelines from learned societies.

The proposals to amend the product information by removing text in the SmPC section 4.6 and 5.1 regarding use of HES solutions for infusion in the context of Caesarean section were not considered to have a substantial impact on prescribers' behaviour. In particular, the proposed amendments will not prevent deliberate use, in view of local clinical protocols (e.g. use in a prophylaxis setting).

Update of national or European therapeutic guidelines from recognised learned societies is beyond the measures that can be formally implemented by the EMA, the European Commission or the competent authorities of the EU Member States. The feasibility and whether it could be achieved within a reasonable timeframe proportionate to the identified serious risks associated with exposure in contraindicated settings is also questioned. These therapeutic guidelines are defined by learned societies, not by the national competent authorities or the MAHs.

The PRAC also noted, based on information from the MAHs of an expected further reduction of accredited sites and limited interest of sites to participate in a DUS, that an additional study to measure adherence to the proposed revised additional RMMs may not yield meaningful results, thereby rendering it impossible to measure if future patients would be treated according to the product information.

Overall conclusion

The PRAC considered that adherence to the RMMs imposed in referrals under Article 107i (EMEA/H/A-107i/1376) in 2013 and Article 107i (EMEA/H/A-107i/1457) in 2018 is critical to ensure a positive benefit-risk balance of the HES solutons for infusion. However, HES solutions for infusion are still used in contraindicated populations including patients being critically ill, with renal impairment or patients with sepsis, and that the estimated level of continued usage in these populations where serious harm has been demonstrated, including an increased risk of mortality, raises important public health concerns. Information provided within this procedure shows that the non-adherence is not only due to a lack of awareness of the restrictions among prescribers, rendering further communication, education and the other proposed measures unlikely to be sufficiently effective.

The PRAC concluded that no further RMMs, or combination of RMMs, could be identified to sufficiently ensure safe use of HES solutions for infusion.

Additional data from the literature (randomized controlled clinical trials and meta-analyses) and post marketing spontaneous reports (decreased reporting rates over ten years) were thoroughly discussed as well as the number of certified HCPs and accredited hospitals. These elements did not raise any new point that was not already addressed in previous procedures such as the latest PSUSA in (October PRAC in 2021) and the referral in 2018.

In view of the seriousness of the safety issues and that the proportion of patients who are exposed to these risks in the absence of effective RMMs could have important public health consequences

including a potentially increased mortality, the PRAC concluded that the benefit-risk balance of hydroxyethyl starch solutions for infusion is no longer favourable and recommended the suspension of the marketing authorisations.

A DHPC is considered warranted to inform HCPs about the upcoming suspension of the marketing authorisations in the concerned EU Member States.

3. Recommendations

Based on the PRAC review of the PASS final study report version 2.0, the PRAC considers by majority decision that:

☒ the benefit-risk balance of medicinal products containing the active substance hydroxyethyl starch concerned by the PASS final report is negative and recommends the suspension of the marketing authorisation(s) on the following grounds:

Grounds for suspension

Whereas,

- The Pharmacovigilance Risk Assessment Committee (PRAC) conclusions of the reviews under Article 31 of Directive (EMEA/H/A-31/1348) and Article 107i of Directive 2001/83/EC (EMEA/H/A-107i/1376) which were finalized in 2013, were that hydroxyethyl starch (HES) solutions for infusion increase risk of mortality and renal failure in patients with sepsis or being critically ill, and therefore, these populations should be contraindicated.
- In the subsequent procedure under Article 107i of Directive 2001/83/EC (EMEA/H/A-107i/1457), a combination of new risk minimisation measures to effectively ensure that HES solutions are not used in patients at risk for serious harm such as patients with sepsis or being critically ill were introduced.
- In the current procedure under Article 107q of Directive 2001/83/EC, for HES solution for infusion, the PRAC assessed the final results of a Drug Utilisation Study (DUS, EUPAS32145) to evaluate the effectiveness of the risk minimisation measures introduced in 2018 in the referral procedure EMEA/H/A-107i/1457.
- The PRAC reviewed the submitted final results of the DUS (EUPAS32145), as well as responses submitted by the marketing authorisation holders (MAHs) in writing and at an oral explanation, which included proposals for further risk minimisation measures.
- The PRAC concluded that non-adherence to the product information remains despite the extensive additional risk minimisation measures, which were implemented as an outcome of the previous referral procedure in 2018. In particular, the PRAC was concerned about the continued high non-adherence to contraindications as reported in the current DUS, which constituted 6.6% of all non-adherent prescriptions. This included 3.5% prescriptions for critically ill patients, 2.2% prescriptions for patients with renal impairment and approximately 1% for patients with sepsis. Moreover, the PRAC was concerned about the high overall non-adherence to the product information observed in four Member States (ranging from 81.6 % to 94.1 % in Belgium, Italy and the Netherlands and 39.9% in France).

- The PRAC noted the general adherence to the recommended dose and duration of treatment. However, the PRAC concluded that it is not possible to identify a cut-off level below which harm is avoided in vulnerable populations, and that evidence demonstrating harm is seen in patient groups treated at doses consistent with the current recommendations. Therefore, it cannot be concluded that the use in contraindicated patients seen in the DUS is safe because of the dose regimens used.
- In view of the results from the current DUS, the PRAC concluded that HES is still used in contraindicated populations including patients being critically ill, with renal impairment or patients with sepsis, and that the estimated level of continued usage in these populations where serious harm has been demonstrated, including an increased risk for mortality, raises important public health concerns.
- The PRAC considered further risk minimisation measures to reduce the non-adherence to the product information in place for HES solutions for infusion. This included changes to the product information, and to the controlled access programme such as further restrictions in supply, an engagement letter, revision of training material, mandatory annual recertification and post-training testing of health care professionals, annual re-certification of hospitals, mandatory entry of some patient information into a database in a few selected Member States where the highest non-adherence was observed in the DUS, as well as further communication via a DHPC. However, information provided within this procedure shows that the non-adherence is not only due to a lack of awareness of the restrictions among prescribers, rendering further communication, education and the other proposed measures unlikely to be sufficiently effective. The PRAC also noted, based on information from the MAHs of an expected further reduction of accredited sites and limited interest of sites to participate in a DUS, that an additional study to measure adherence to the proposed revised additional risk minimisation measures may not yield meaningful results, thereby rendering it impossible to measure if future patients would be treated according to the product information. The PRAC concluded that no further risk minimisation measure, or combination of risk minimisation measures, could be identified to sufficiently ensure safe use of HES solutions for infusion. In view of the above, the PRAC concluded that pursuant to Article 116 of Directive 2001/83/EC the risks related to the use of HES outweigh their benefits and thus the benefit-risk balance of HES solutions for infusion is no longer favourable.

Therefore, the PRAC recommends the suspension of the marketing authorisations for all medicinal products referred to in Annex I to the PRAC recommendation.

The condition imposed to lift the suspension of the marketing authorisation is as follows:

Condition to lift the suspension

For the suspension to be lifted, the Marketing Authorisation Holder(s) shall provide robust scientific evidence showing a positive benefit-risk balance in a clinically relevant patient population(s), together with a set of risk minimisation measures that can sufficiently protect patients at an increased risk of serious harm from being exposed to HES solutions for infusions.

Appendix 1

PRAC Divergent position

DIVERGENT POSITION

Procedure No: EMEA/H/N/PSR/J/0031

hydroxyethyl starch (HES) solutions for infusion

Divergent statement

The undersigned member(s) of the PRAC did not agree with the PRAC's positive recommendation recommending the suspension of the nationally authorised medicinal product(s) containing hydroxyethyl starch (for details see PRAC assessment report).

The reason for divergent opinion was the following:

A Joint Drug Utilisation Study (JDUS) was submitted in fulfilment of conditions to the marketing authorization following procedure EMEA/H/A-107i/1457. This study assessed the effectiveness of the new set of risk minimisation measures (RMMs) on the non-adherence to the approved European PI regarding indication, contraindication and posology. The JDUS recruited 1851 patients fulfilling the study eligibility criteria for 1863 prescriptions in 32 sites/hospitals across European countries.

The results of the JDUS show that there was a reduction in overall non-adherence to 23.91% compared to 69% - 77.5% in previous DUSs mandated, following the previous EU Article 31 (EMEA/H/A-31/1348) and 107i (EMEA/H/A-107i/1376) referral procedures.

An 18.85% of non-adherence pertained to indications which was driven specifically by high non-adherence rates observed in some MSs (BE 94%, IT 81%, NL 85% and FR 39.9%) as compared to DE 5.7%, PL 26%, ES; CZ & HU, with less than 20% of non-adherence. Although the results suggest that the RMMs are not well fitted to all countries/sites, they have worked quite well in some other countries. The further measures proposed by the MAHs in this procedure aim at improving the non-adherence of practitioners related to the currently implemented controlled access program, are expected to leave a huge impact on the practice and are sufficient to counteract the diffuse practice of off-label use. These measures are focused not only on raising awareness of HCPs but also on the prevention of product delivery to departments that previously administered HES incorrectly as well as on the restriction of delivery (by hospital pharmacies) of HES-containing product to Anaesthesia and Emergency departments only. The re-certification of centers will limit the use of the product only where acute blood loss occurred, thereby further improving adherence to the PI.

Key to the benefit-risk for Poly(O-2-hydroxyethyl) starch (HES) are also consideration of the following:

The results of the JDUS show that the median HES dose was 500 mL (6.76 mL/kg), and that the median treatment duration was 0.583 hours with almost all patients receiving only a single prescription. Therefore, this short duration of use as seen in the JDUS results has a minimal risk of kidney injury. In addition, the results of non-adherence to contraindications of 6.5% (significantly decreased compared to the results of previous DUS) could be further minimized by the MAHs' proposals. Also, the proposals of the MAHs further reassure that the concerns raised in the Art. 31 referral in 2012 (EMEA/H/A-31/1348) and in Art.107i referral in 2013 (EMEA/H/A-107i/1376) are being effectively resolved.

Moreover, when assessing the B/R profile of HES, the results of DUS should be further completed with all other new information. After the assessment of the last PSUSA for HES in November 2021

(PSUSA 00001694/202103) the PRAC agreed on unchanged B/R profile (i.e. positive). Since that time, based on available information from published studies and ADR reports, no new important safety information was identified that could modify the current benefit/risk balance.

It is considered that the suspension of marketing authorisation of HES-containing medicinal products is currently not risk proportionate and could lead to an unmet medical need in some severe hypovolemic situations.

Therefore, taking into account the results obtained within the framework of the DUS together with all other available information on safety and efficacy, the benefit-risk balance of the HES products remains unchanged.

PRAC Members expressing a divergent opinion:

Eva Jirsová	10 February 2022
Sophia Trantza	10 February 2022
Melinda Palfi	10 February 2022
John Joseph Borg	10 February 2022
Roxana Dondera	10 February 2022
Marek Juracka	10 February 2022
Eva A. Segovia	10 February 2022
Milena Radoha-Bergoc	10 February 2022
Tiphaine Vaillant	16 February 2022