HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

29 October 2014

VOLUVEN, solution for infusion

1 × 500 ml PVC Perfuflex bag (CIP: 34009 356 738 0 0)
1 × 500 ml polypropylene/SIS-polypropylene/styrene-ethylene-butadiene bag (CIP: 34009 367 404 1 9)

Applicant: FRESENIUS KABI France

INN	Hydroxyethyl starch 130/0.4 Sodium chloride
ATC Code (2013)	B05AA07 (blood substitutes and plasma protein fractions)
Reason for the review:	**Reassessment of Actual Benefit at the request of the Committee, in accordance with Article R 163-21 of the Social Security Code.**
List concerned	**Hospital use** (French Public Health Code L.5123-2)
Indication concerned	**"Treatment of hypovolaemia due to acute blood loss when use of crystalloids alone is considered inadequate."**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Initial Marketing Authorisation (procedure)	4 April 2001 (national procedure)
Revisions	Revisions of 30 April 2014 following reassessment of the risk-benefit ratio by the EMA.
Prescribing and dispensing conditions /special status	Non-prescription medicine (hydroxyethyl starch not listed) Medicines under enhanced surveillance: post-marketing safety study requested by the PRAC.

ATC Classification	2013	
	B:	Blood and blood forming organs
	B05:	Blood substitutes and perfusion solutions
	B05A:	Blood and related products
	B05AA:	Blood substitutes and plasma protein fractions
	B05AA07:	Hydroxyethyl starch

02 TRANSPARENCY COMMITTEE CONCLUSIONS

02.1 Actual benefit

◗ Hypovolaemia due to acute blood loss is potentially life-threatening.
◗ This proprietary medicinal product is intended as curative treatment for hypovolaemia.
◗ It is a second-line treatment when use of crystalloids alone is considered inadequate.
◗ The efficacy/adverse effects ratio of this medicinal product has not been clearly established, given the incidence of renal failure and higher mortality seen in patients with sepsis or in intensive care and the uncertainty surrounding the safety of HES in hypovolaemia due to acute blood loss.
◗ There are treatment alternatives, in particular albumin.

Taking account of these points, the Committee considers that VOLUVEN has a moderate actual benefit after an inadequate response to crystalloids in the new Marketing Authorisation indication, solely in patients who have undergone surgery or for management of acute blood loss.

The Committee recommends continued inclusion of VOLUVEN on the list of medicines approved for hospital use in the indication "treatment of hypovolaemia due to acute blood loss when use of crystalloids alone is considered inadequate" and at the dosages in the Marketing Authorisation.

APPENDIX 1

ASSESSMENT REPORT

01 THERAPEUTIC INDICATION

“Treatment of hypovolaemia due to acute blood loss when use of crystalloids alone is considered inadequate.”

02 DOSAGE

“Use of HES must be limited to the initial stage of plasma volume expansion, with a maximum duration of 24 h.

The dosage depends on the degree of hypovolaemia and on the patient's age, weight and haemodynamic status.

The maximum daily dose is 30 ml/kg.

The lowest effective dose should be administered. Treatment must be given under continuous haemodynamic monitoring so that infusion can be stopped as soon as the haemodynamic target is reached. The maximum recommended dose must not be exceeded.

Paediatric population
Data in children are limited, therefore use of hydroxyethyl starch is not recommended in this population.

Method of administration
Strictly for intravenous infusion.
The infusion volume and rate depend on the degree of hypovolaemia and must be adapted to the clinical and cardiovascular state of the patient.
The first 10 to 20 ml of solution should be infused slowly, monitoring the patient closely to ensure that any anaphylactoid reaction is detected as swiftly as possible.”

03 SUMMARY OF PREVIOUS ASSESSMENTS

See table below.

1 Table 1: Reassessed proprietary medicinal products, former wording of the Marketing Authorisation and previous conclusions of the TC

Name *Company*	INN	Indication Date of Marketing Authorisation) Inclusion on list for hospital use	Conclusion of studies submitted to the Committee	Transparency Committee conclusions (AB/IAB/Date of opinion)
PLASMAVOLUME 6% BAXTER	HES 130/0.42 In Ringer's acetate solution	Treatment of acute or manifest hypovolaemia and of hypovolaemic shock Marketing Authorisation 4 April 2001 Included on the list of medicines approved for hospital use since 8 July 2009	In a controlled clinical study, no difference in volume expansion efficacy (volumes infused and haemodynamic parameters) was demonstrated between PLASMAVOLUME 6% (HES 130/0.42/6:1) and a standard HES solution (130/0.42) in 62 abdominal or urological surgery patients. It has not been established whether PLASMAVOLUME 6% offers any additional clinical benefit over other plasma volume expanders. The safety profile of PLASMAVOLUME 6% does not appear to differ from that of other HES products.	Substantial AB No IAB over other medicinal products in this class (HES). (13 May 2009)
RESTORVOL 6% B BRAUN	HES 130/0.42 In sodium chloride solution	Prophylaxis and treatment of hypovolaemia, particularly when repeated infusions are necessary. Marketing Authorisation 15 February 2008 Included on the list of medicines approved for use by hospitals since 21 October 2008	In a controlled clinical study, equivalence in volume expansion efficacy (volumes infused and haemodynamic parameters) was demonstrated between RESTORVOL 6% (HES 130/0.42/6:1) and a standard HES (200/0.5) in 60 gynaecological surgery patients. Because of its physicochemical characteristics (molecular weight, degree of molar substitution and C2/C6 ratio), RESTORVOL 6% could in theory lower the toxicity, in particular renal, of such products. However, no difference in adverse effects was demonstrated between RESTORVOL and standard HES products (200/0.5) according to the available data. There have not been any clinical studies directly comparing the volume expansion efficacy and/or safety of RESTORVOL 6% with that of VOLUVEN (the HES with the closest composition, but a C2/C6 ratio of 9:1). The safety profile of RESTORVOL 6% does not appear to differ from that of other HES products.	Substantial AB No IAB over other medicinal products in this class (HES). (25 June 2008)
VOLUVEN 6% FRESENIUS KABI	HES 130/0.42 In sodium chloride solution	Prophylaxis and treatment of hypovolaemia, particularly when repeated infusions are necessary. Marketing Authorisation 4 April 2001 Included on the list of medicines approved for use	Two trials comparing VOLUVEN with HESTERIL 6%, carried out on one day, included 100 orthopaedic surgery patients (study 1) and 59 cardiac surgery patients (study 2) respectively. In these two studies the primary efficacy endpoint was the efficacy of volume expansion as estimated by the total amount of hydroxyethyl starch infused. The efficacy of the two hydroxyethyl starch products was comparable in the two groups in the two studies. Opinion of 5 September 2001	Substantial AB No IAB over HESTERIL 6% (5 May 2005)

		by hospitals since 26 October 2001	An open-label randomised comparative study of 42 abdominal surgery patients compared single doses of VOLUVEN and GELOFUSINE 4% in terms of haemodynamic efficacy and haematological safety. The methodological limitations of this study (open-label study, small patient population) mean it is not possible to draw any conclusions as regards the non-inferiority of VOLUVEN versus GELOFUSINE. Opinion of 5 May 2005 A double-blind randomised comparative study compared VOLUVEN with HESTERIL 6% in combination with 5% albumin in patients with head injuries. In terms of clinical efficacy, VOLUVEN resulted in a decrease versus HESTERIL in the duration of ventilation, duration of plasma volume replacement and in the number of patients with intracranial hypertension. However, given the small number of patients who underwent evaluation here (15 patients per group), these results must be interpreted with caution. These results were obtained with co-administration of human albumin. Moreover, the amount of colloid infused, mortality and need for transfusions of blood products were comparable in the two arms. Opinion of 5 May 2005	
ISOVOL 6% B BRAUN	HES 130/0.42 In a balanced electrolyte solution.	Prophylaxis and treatment of hypovolaemia, particularly when repeated infusions are necessary, while maintaining electrolyte and acid-base homeostasis. Marketing Authorisation 8 November 2011 Application made for inclusion on the list of medicines approved for hospital use.	Under assessment	

04 BACKGROUND AND PURPOSE OF THE REASSESSMENT

The Transparency Committee (TC) of HAS assesses medicinal products that have obtained Marketing Authorisation (MA) when the company marketing them wishes them to be included on the list of refundable medicines (articles L.162-17 of the French Social Security Code and L.5123-2 of the French Public Health Code) or on request.

The TC is a scientific body composed of medical practitioners, pharmacists and specialists in methodology and epidemiology.
Its objectives are:

- to provide an opinion to ministers responsible for health and social security on the justification for reimbursement of medicinal products by social security and/or for their use in hospitals, with particular regard to their actual benefit (AB) and to the improvement in actual benefit (IAB) they are likely to offer compared with treatments that are already available;
- to contribute to the proper use of medicinal products by publishing relevant and independent scientific information on the products.

These objectives are defined in the French Social Security Code, in particular in articles R.163-2 to R.163-21, L.161-37, L.161-39 and L.161-41.
According to articles L. 162-17, L. 161-37, L.161-39, L. 161-41, L. 161-44, R. 163-2 to R. 163-21, R. 161-71, R. 161-76 and R. 161-85 of the French Social Security Code and articles L. 5123-2 and L. 5123-3 of the French Public Health Code, the opinions of the TC specify the actual benefit and improvement in actual benefit provided by the medicinal products.
This assessment is performed on the basis of a critical analysis of scientific data obtained through evidence-based medicine and the opinion of experts, in accordance with the indications and dosages in the Marketing Authorisation.

The reassessment of HES products relates to four proprietary medicinal products, for which dossiers have been submitted by the manufacturers. These proprietary medicinal products and the previous conclusions of the Transparency Committee are shown in the table below.

Three other proprietary medicinal products have Marketing Authorisation and are approved for hospital use. At the request of the manufacturers, these will be the subject of a removal Opinion. The proprietary medicinal products concerned are:

- PLASMOHES 6%, manufactured by AGUETTANT (HES 200/0.5)
- HEAFUSINE 6%, manufactured by B BRAUN (HES 200/0.5)
- HYPERHES solution for infusion, manufactured by FRESENIUS KABI France (HES 200/0.5).

04.1 History and background to the reassessment

4.1.1 European reassessment

In December 2012, following the publication of two clinical trials[1,2] that showed an increase in renal impairment associated with use of HES and concerns about higher mortality, the EMA undertook a reassessment of the relative risks and benefits of HES as a class.

[1] Myburgh J.A. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 2012; 367: 1901-11
[2] Perner A. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 2012; 367: 124-34

In June 2013, the PRAC[3] concluded that the benefits did not outweigh the risks and recommended the suspension of the Marketing Authorisation of these proprietary medicinal products.

On 10 October 2013, after examining new data as part of on appeal procedure, the PRAC concluded that proprietary medicinal products containing HES must be limited to a restricted group of patients. This position was approved by the CMDh,[4] who proposed amendments to the SPC (in particular the restriction of the indication to "treatment of hypovolaemia due to acute blood loss when use of crystalloids alone is considered inadequate"). In France this information was published on the ANSM website on 12 November 2013 in a "Patient Safety Information" letter sent by the manufacturers to healthcare professionals under the authority of the ANSM. The companies concerned have agreed to carry out additional studies on the efficacy and long-term safety of these medicinal products.

On 30 April 2014 the ANSM issued revised Marketing Authorisations for proprietary medicinal products containing HES, in which the indication, dosage, contraindications and warnings have been updated. The revised Marketing Authorisations also detail the additional studies that the manufacturers were asked to provide (see section 11).

Use of proprietary medicinal products containing HES is now permitted only in the "treatment of hypovolaemia due to acute blood loss when use of crystalloids alone is considered inadequate" and at the lowest effective dose and for the shortest possible duration. Treatment must be given under continuous haemodynamic monitoring so that infusion can be stopped as soon as the haemodynamic target is reached.

Proprietary medicinal products containing HES are now contraindicated in the following situations:

- sepsis,
- patients with burns,
- renal failure and in dialysis patients,
- intracranial or cerebral haemorrhage,
- patients in critical/intensive care,
- fluid overload,
- pulmonary oedema,
- dehydration,
- severe hypernatraemia or severe hyperchloraemia,
- severe hepatic impairment,
- congestive heart failure,
- severe coagulopathies,
- organ transplant patients.

In the absence of data supporting long-term safety in patients undergoing surgery and in trauma patients, the expected benefit of this treatment must be carefully assessed given the uncertainties about its long-term safety. The available treatment alternatives must be considered.

Large randomised clinical studies have shown an increased risk of renal impairment in intensive-care patients, including patients with sepsis. HES products must therefore not be used in such patients.

Monitoring of renal function is recommended in patients being treated with proprietary medicinal products containing HES and their use must be suspended at the first sign of renal impairment.

[3] The PRAC [Pharmacovigilance Risk Assessment Committee] is an EMA committee.

[4] The CMDh [Coordination Group for Mutual Recognition and Decentralised Procedures – Human], represents the member states of the European Union. This is an HMA [Heads of Medicine Agencies] group and is a network of European authorities on medical matters.

4.1.2 Reassessment of HES by the Transparency Committee

In May 2013 the renal adverse effects and concerns about higher mortality associated with use of HES products were brought to the attention of the Transparency Committee.

The objective of this reassessment is to reassess the benefit of HES products as regards their renal adverse effects and new mortality data in respect of treatment alternatives and therapeutic need in the treatment of hypovolaemia due to blood loss.

05 THERAPEUTIC NEED

Hypovolaemia is a condition typically treated in patients receiving emergency or intensive care.

It may be absolute hypovolaemia resulting from haemorrhage or from decreased plasma volume due to excessive fluid and sodium loss or to extravasation of water and sodium into the interstitial tissues. Hypovolaemia may also be relative in septic shock, anaphylactic shock, general or local/regional anaesthesia or in some cases of intoxication, particularly with CNS depressants. Only hypovolaemia due to blood loss may be treated with a HES.

In the event of major blood loss, a rapid transfusion is often essential. However, while waiting for this to be carried out or in cases where this is not indicated, treatment with a plasma volume expander is necessary.

There are two main categories of volume expander: crystalloids, the effect of which is due to their osmolality (isotonic or hypertonic salt solutions, Ringer's solution, etc.), and colloids, which include synthetic colloids (HES, dextrans, gelatins) and a natural colloid, albumin. The effect of colloids is due essentially to their oncotic pressure.

Colloids, which have the benefit of requiring smaller volumes, have a more rapid effect than crystalloids. Their drawback is their numerous adverse effects.[5]

- "All colloids carry a risk of allergy, but with an incidence of serious reactions no greater than one in a thousand patients. This risk is greatest with gelatins and lowest with albumin and HES.
- Dextrans can cause haemostatic disturbances.
- Although albumin has not thus far been shown to be responsible in any cases of known transmission of viral pathogens or of other, non-conventional transmissible agents, it cannot be regarded as having zero biological risk given that it is a product of human origin.
- Although gelatins have not thus far been shown to be responsible in any cases of diseases caused by non-conventional transmissible agents, such as Creutzfeldt-Jakob disease, they cannot be regarded as having zero biological risk given that they are bovine in origin."

The SFAR [French Society of Anaesthesia and Intensive Care] guidelines updated in April 2013 (before the amendment to the Marketing Authorisation for HES products), were as follows:

- "The use of albumin is justified only when use of synthetic colloids is contraindicated or in hypoproteinaemia < 35 g/l (not resulting from dilution of plasma proteins through prior infusion of synthetic colloids).
- Among colloids, it is recommended to use a hydroxyethyl starch, which have fewer side effects than gelatins and are plant-based.
- Among crystalloids, it is recommended to use isotonic crystalloids and, by preference, Ringer's lactate, except in patients with hepatic impairment, serious head injury or hyperkalaemia."

[5] SFAR. Treatment with plasma volume expanders in relative or absolute hypovolaemia. SPC 1997 posted online on 16 December 2002 and amended on 11 April 2013. www.sfar.org

06 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

In the United States, HES products are refundable with restrictions. On 25 November 2013, the FDA published on its website the conclusions of its reassessment of HES products based on a literature review.[6] Its conclusions were as follows:
Studies point to an increase in mortality and in the need for renal replacement therapy (dialysis or transplant) in severely ill patients treated with HES, including patients with sepsis. This is a class effect. The FDA concluded that HES products must not be used in such patients and that a warning (boxed warning) was necessary to inform patients and healthcare professionals of this risk:

- Do not use HES products in patients in a critical condition, particularly in patients with sepsis or being treated in a hospital intensive care unit.
- Avoid using HES products in patients with existing renal impairment.
- Suspend treatment with HES at the first sign of renal impairment.
- Monitor renal function for at least 90 days in all patients, as a need for renal substitution has been observed up to 90 days after administration of HES.

07 CLINICALLY RELEVANT COMPARATORS

The comparators for HES products are other synthetic colloid solutions: dextran, gelatins, natural colloids (albumin) and other solutes of the crystalloid class.

INN or TC	Name	Indication concerned	AB (IAB)	Reimbursed
Colloids				
Dextran	RESCUEFLOW	Initial treatment of hypovolaemia with hypotension in traumatic shock	Substantial	Hospitals
Gelatin	GELASPAN GELOFUSINE PLASMION	Prophylaxis and treatment of relative or absolute hypovolaemia and imminent or manifest shock Emergency treatment of states of shock	Substantial	Hospitals
Albumin	ALBUNORM VIALEBEX VIALEBEX YDRALBUM	Restoration and maintenance of circulating blood volume when loss of volume has been demonstrated and use of a colloid is appropriate	Substantial	Hospitals
Crystalloids				
Ringer and Ringer's lactate	Numerous proprietary medicinal products	Hypovolaemia	Substantial (IAB V)	National Insurance and hospital use
Isotonic and hypertonic sodium chloride solutions	Numerous proprietary medicinal products	Hypovolaemia	Substantial (IAB V)	National Insurance and hospital use

◗ Conclusion

All the comparators listed are clinically relevant.

[6] FDA Safety Communication: Boxed warning on increased mortality and severe renal injury, and additional warning on risk of bleeding, for use of hydroxyethyl starch solutions in some settings. November 25, 2013 http://www.fda.gov/biologicsbloodvaccines/safetyavailability/ucm358271.htm

08 DATA SEARCH

This reassessment of hydroxyethyl starches as a class is based on the data and conclusions of the PRAC. The initial conclusions of the PRAC were issued in November 2013. In addition, HAS has carried out a literature search via PubMed up to April 2014.

The manufacturers have also been asked to provide HAS with all the available clinical data necessary to reassess the actual benefit of HES as a class and a summary of the existing data.

09 CLINICAL DATA

09.1 Initial efficacy data

The conclusions of the initial data that had led to inclusion of HES products that are the subject of this reassessment are presented in Table 1.

The majority of these are comparative studies versus the initial HES products included in the list of medicines approved for use in hospitals and now withdrawn. These studies are methodologically poor quality, open-label by definition, and carried out on small patient populations. The efficacy endpoints were intermediate endpoints; in particular none of these studies examined short- or medium-term mortality.

09.2 Literature data on mortality and renal safety

The starting point of the reassessment of HES products as a class was the publication of three studies in 2008 and then 2012 that showed an increased risk of renal impairment and concerns about increased mortality with HES.

- A German randomised open-label study (VISEP) published in 2008 by Brunkhorst,[7] in patients being treated in a hospital intensive care unit on account of severe sepsis compared intensive insulin therapy with conventional insulin therapy and HES 200/0.5 with Ringer's lactate in a two-by-two design. The primary efficacy endpoints were 28-day mortality and mean SOFA (Sequential Organ Failure Assessment) score. The trial was stopped prematurely on safety grounds. In the 537 patients evaluated, no significant difference was found between the two groups in 28-day mortality or in organ failure score, whereas the proportion of patients suffering renal failure or requiring dialysis was higher in the HES group (10.9%) than in the Ringer's lactate group (5.2%) (p=0.01).

- A Scandinavian randomised single-blind study (6S) published in July 2012 by Perner[2] compared the effects of infusion of HES with that of Ringer's solution in 804 patients being treated in a hospital intensive care unit on account of severe sepsis. The primary endpoint was death or renal failure still requiring dialysis after 90 days. After 90 days, 51% of patients treated with HES and 43% of patients treated with Ringer's solution had died (RR = 1.17, 95% CI [1.01-1.36], p=0.03). Dialysis on account of renal failure was still necessary in 22% in the HES group and in 16% in the Ringer's acetate group (RR = 1.52, 95% CI [0.94-2.48]; p=0.09).

- The Australian randomised, blinded CHEST[1] study published in November 2012 compared HES 130/0.4 treatment with a saline solution in 7000 patients being treated in intensive care units (inclusion of all patients requiring treatment with a plasma volume expander on account

[7] Brunkhorst FM. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008, 358: 125-139

of hypovolaemia over a defined period). No difference in 90-day mortality was observed between the groups (18% in the HES group and 17% in the saline solution group; RR = 1.06, 95% CI [0.96-1.18], p=0.26). Among the secondary endpoints, renal support equipment was used in 7.0% of patients in the HES group and in 5.8% of patients in the saline solution group (RR = 1.21, 95% CI [1.00-1.45], p=0.04). Patients developed renal failure (decrease ≥ 75% in glomerular filtration rate) in 10.4% of cases treated with HES and in 9.2% of cases given saline solution (p=0.12).

To address the question of higher mortality in patients in situations other than sepsis, a number of meta-analyses were published in 2013:

- The Canadian meta-analysis by Zarychanski[8] compared the mortality and renal safety of HES with that of other plasma volume expander solutions in 10,290 patients receiving emergency or intensive care treatment, including for sepsis and trauma. The results show that with HES there was an increased risk of death (RR = 1.09, 95% CI [1.02-1.17] I^2 = 0%), an increased risk of renal failure (RR = 1.27, 95% CI [1.09-1.47], I^2 = 26%) and an increased need for renal support equipment (RR = 1.32, 95% CI [1.15-1.50], I^2 = 0%).

- The meta-analysis by Perel[9] published in the Cochrane review compared mortality when colloids are used in patients in a serious condition (trauma, burns, following surgery, septic shock) requiring administration of a plasma volume expander solution with that of crystalloids. Preoperative patients were excluded. In the subgroup of studies that compared an HES product with a crystalloid (25 studies/9147 patients), the results showed an increased risk of mortality (RR = 1.10, 95% CI [1.02-1.19]).

- In the Australian meta-analysis by Gattas,[10] the studies included compared at least one group receiving HES130/0.4 with another group receiving either a crystalloid, another colloid, or another HES of different character. The studies examined included pre- or perioperative patients and patients treated in hospital intensive care units irrespective of the reason. The efficacy endpoints were mortality and need for renal support equipment.
  In the subgroup of 11 studies that compared a HES 130/0.4 with a crystalloid, there was no observed difference in mortality (RR = 1.08, 95% CI [0.97-1.21], I^2 = 12.1%) and renal support equipment was needed more often in the group treated with HES 130/0.4 than in the group treated with a crystalloid (RR = 1.27, 95% CI [1.10-1.46] I^2 = 0.0%).

In two of the three meta-analyses covering different situations, the 90-day mortality was higher in the patients treated with HES than in the patients treated with crystalloids. The magnitude of the increased relative risk of mortality was approximately 1.1 in all three meta-analyses irrespective of clinical context.
The CRISTAL[11] study is a randomised open-label study of 2857 patients that compared different colloids (gelatin, dextran, HES or albumin) with crystalloids (Ringer's solution, isotonic or hypertonic saline solution). The patients included had either sepsis, multiple trauma or hypovolaemic shock of other cause. The primary endpoint was 28-day mortality and the secondary endpoint 90-day mortality. After 28 days no difference was observed between the two groups, with 27% deaths in the crystalloid group and 25.4% in the colloid group (RR = 0.96, 95% CI [0.88-1.04]). After 90 days, mortality was 30.7% in the colloid group and 34.2% in the crystalloid group (RR = 0.92, 95% CI [0.86-0.99]. However, this study was affected by bias (open-label study,

[8] Zarychanski R. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation. JAMA 2013, 309: 678-88.
[9] Perel P. Colloids versus crystalloids for fluid resuscitation in critically ill patients. 2013 The Cochrane collaboration. www.thecochranelibrary.com
[10] Gattas J. Fluid resuscitation with 6% hydroxyethyl starch (130/0.4 and 130/0.42) in acutely ill patients : systematic review of effects on mortality and treatment with renal replacement therapy. Intensive Care Med 2013; 39: 558-68
[11] Annane D. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. JAMA. 2013 Nov 6; 310 (17): 1809-17

non-comparability of the groups in terms of treatment of hypovolaemia prior to inclusion) and its results on their own cannot therefore be considered to contradict the earlier findings.

The other studies presented in the dossiers submitted by the manufacturers and the more recent studies are not of sufficiently good methodological quality to be discussed here or do not address the questions posed by this reassessment, i.e. as regards renal safety and mortality. The principal methodological limitations observed are the lack of randomisation, a follow-up period that was too short (for a period of days only) to evaluate mortality or an insufficient number of patients to be able to draw any conclusions.

09.3 Usage data for HES products

According to 2014 data from the GERS [French Group for the Elaboration and Implementation of Statistics], the number of bags of VOLUVEN sold to hospitals in 2013 has decreased steadily, going from 100,000 bags per month in January 2013 to 34,000 per month in March 2014.
Sales of PLASMAVOLUME and HYPERHES, which were both still on the market at the start of 2012, have gradually ceased over the course of 2012 and 2013.
There are no available hospital sales data for RESTORVOL (still on the market as of this year).

010 SUMMARY AND DISCUSSION

Following the reassessment of the relative risks and benefits by the EMA, the objective of the reassessment of HES products by the Transparency Committee is to reassess the clinical benefit of HES in the light of their renal adverse effects and new mortality data in relation to therapeutic need in the treatment of hypovolaemia due to blood loss.

The initial efficacy data are of poor methodological quality: small patient populations, open-label study by definition and based on intermediate endpoints.

In recent years there have been many published studies on renal safety and medium-term mortality (1-3 months). The VISEP, 6S and CHEST studies were the first to conclude that HES products have a harmful effect on the kidneys in sepsis and in intensive care patients and result in increased 90-day mortality in patients with sepsis. However, although unable to draw any firm conclusions, they did cast doubt over whether increased mortality due to HES is observed in all causes of hypovolaemia.

Following on from this, three 2013 meta-analyses studied mortality in different hypovolaemia situations. These confirmed all the effects of HES as regards an increased need for dialysis compared with crystalloids. Two of them demonstrated increased mortality (RR = 1.09, 95% CI [1.02-1.17] and (RR = 1.10, 95% CI [1.02-1.19], whereas the third meta-analysis found the results to be not significant (RR = 1.08, 95% CI [0.97-1.21], but close to the significance threshold and not much different to the other two (relative risk of the order of 1.1).

In October 2013, a new randomised open-label clinical trial (CRISTAL) in 2857 patients in hypovolaemic shock of diverse causes was found to contradict the earlier findings. The results showed no difference in 28-day mortality, but the 90-day mortality was higher with crystalloids, with death observed in 30.7% of cases in the colloid group and in 34.2% in the crystalloid group (RR = 0.92, 95% CI [0.86-0.99].

There are no mortality or medium-term renal safety data on the use of crystalloids in the current indication of HES products, i.e. hypovolaemia due to acute blood loss when use of crystalloids alone is considered inadequate.

In conclusion, all of these results point to an increase in 90-day mortality risk associated with use of HES of the order of 1.1 in sepsis and in intensive care patients. However, in the absence of studies on mortality and safety in the current indication of hypovolaemia due to acute blood loss and given the recent publication of the CRISTAL study, which appears to contradict these results, extrapolation of the demonstrated increase in mortality to all hypovolaemia situations and in particular to hypovolaemia due to blood loss, for which there have been no medium-term safety studies, remains open to doubt.

011 STUDY PROGRAMME

The EMA asked the four companies marketing HES products to carry out the following studies:

- Two randomised phase IV clinical trials with an appropriate comparator and clinically significant efficacy endpoints (such as those defined in Annex IV of the European Commission decision of 19 December 2013), to demonstrate efficacy and safety in the perioperative period and after trauma.
  The study protocols must be submitted to the ANSM no later than six months after the European Commission decision.
  The final study report must be submitted to the ANSM before 31 December 2016.

- A study on the use of the medicinal products in several member states, to evaluate the measures to minimise risk that are being taken.
  The study protocols must be submitted to the competent authorities no later than six months after the European Commission decision.
  The final study report must be submitted to the competent authorities no later than 24 months after acceptance of the protocol.

The Marketing Authorisation Holder must submit the core elements of a risk management plan, including the protocol of the study on the use of the medicinal products and the protocols of the randomised clinical trials, no later than six months after the European Commission decision.

The Committee will give due consideration to the results of these studies.

012 THERAPEUTIC USE

In hypovolaemia due to acute blood loss, crystalloids are used as a first-line treatment when required in patients awaiting a blood transfusion. The doses necessary to re-establish satisfactory blood volume do not differ much from those needed with colloids (about 1.4 times higher).

Only in rare cases is it not possible to achieve swift restoration of blood volume with crystalloids. In such patients, albumin or HES may be used. These latter options are reserved for the treatment of acute blood loss that is not relieved by intensive care treatment and to hypovolaemia secondary to surgical intervention, particularly when accompanied by blood loss, if there are no contraindications and if the patient does not respond to intensive care treatment.