Venofundin 60mg/ml Solution for Infusion
Tetraspan 60 mg/ml / Tetraspan 100mg/ml Solution for Infusion
Hemohes 60mg/ml / Hemohes 100mg/ml Solution for Infusion

Active substance(s) (INN or common name):	Poly(O-2-hydroxyethyl)starch
Pharmaco-therapeutic group (ATC Code):	B05AA07
Name of Marketing Authorisation Holder or Applicant:	B. Braun Melsungen AG Carl-Braun-Stasse 1 D-34212 Melsungen
Number of medicinal products to which this RMP refers:	• 5
Product(s) concerned (brand name(s)):	Tetraspan Isohes Equihes Isovol Venofundin Amidolite Restorvol Hemohes Heafusine

Data lock point for this RMP	31.03.2014	Version number	1.0
Date of final sign off	Please see effective date in the header		

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Depleted blood volume in the body (hypovolaemia) due to massive blood loss is a life-threatening condition developed as a result of a variety of medical circumstances. It may either result from bleeding due to trauma, to surgery or to acute bleeding from another underlying disease like cancer, hemorrhage due to rupture of an aneurysm, chronic liver disease, or coagulation disorders. Both external and internal bleeding lead to lowering of blood pressure and make the heart unable to pump enough blood to the body. These changes are accompanied by a reduced perfusion of many organs and tissues, with low supply of nutrients and oxygen, causing them to fail (hypovolaemic shock). The incidence of disease and mortality are correlated to the underlying cause of hypovolaemia.

VI.2.2 Summary of treatment benefits

The administration of intravenous fluids, such as colloid and electrolyte solutions (also called crystalloid solutions), is a common clinical intervention. The B. Braun hydroxyethyl starch solutions (HES solutions) Venofundin 6%, Tetraspan 6% and 10% and Hemohes 6% and 10% are colloid solutions and are used as plasma volume substitutes to restore the blood volume after blood loss when crystalloids alone are not considered sufficient.
Due to their ability to bind water, infusion of HES solutions sustain the blood volume and hence are effectively used to restore and stabilize the blood pressure after massive blood losses due to any cause.
B. Braun Melsungen AG conducted several clinical studies in healthy adults and in surgical patients. In the perioperative setting (e.g. gynaecological, urologic, cardiac and elective surgeries) treatment of hypovolaemia was investigated. An observational study in children showed that HES could safely be used when given in moderate doses.

VI.2.3 Unknowns relating to treatment benefits

There is no evidence for differences in the efficacy of HES solutions in the target population regarding to sex and race. Clinical experience of the intravenous administration in pregnant / lactating women is not available and is limited in the paediatric population.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Allergy (Hypersensitivity)	In rare cases allergic reactions may occur independent of dose. They can be serious and even progress to shock. If an allergic reaction, especially an anaphylactic / anaphylactoid reaction (including swelling of the face, tongue or throat, difficulty in swallowing, hives and breathing difficulties) occurs, your doctor will stop the infusion of HES solution immediately and treat you with basic medical measures. It is not possible to predict by tests which patients may be expected to suffer from an allergic reaction nor to predict the course or the severity of such an allergic reaction.	Do not use HES in case you are allergic to any of the active substances or any of the other ingredients of this medicine.
Delayed graft function (in organ	A transplanted organ is called a graft. After transplantation it will take some time for the graft to regain functionality. During this time	HES should not be used in organ transplant patients. The

Risk	What is known	Preventability
transplant patients)	the patient may need supportive care (e.g. renal replacement therapy or specific medicinal products to increase the urine production in case of kidney transplantation). The time needed for the graft to regain functionality might be prolonged when HES is infused during transplantation surgery or to the brain-dead organ donor.	requirements as regards indication, contraindications, dosage and duration of treatment have to be strictly followed.
Kidney injury (renal injury) (need for renal replacement theraphy up to 90 days after HES administration)	Some published studies in patients admitted to the intensive care unit or in patients with a generalized infection of the body have indicated an increased risk of kidney injury by means of an increased risk to require any kind of renal replacement therapy for up to 90 days after HES infusion.	All requirements as regards indication, contraindications, dosage and duration of treatment have to be strictly followed.
Increased bleeding in patients with coagulation disorders, severely impaired hepatic function, intracranial or cerebral haemorrhage and open heart surgery in association with cardiopulmonary bypass	Infusion of volume replacement solutions such as HES will add additional fluid to the circulatory system thus diluting the blood. Furthermore HES might interact with specific components of the blood clotting system. Dilution of your blood clotting factors present in the blood may in turn cause bleeding complications in patients with pre-existing clotting disorders and in patients undergoing an open heart surgery when the circulatory system is maintained by means of a pumping device or in patients suffering from brain injury associated with bleeding.	All requirements as regards indication, contraindications, dosage and duration of treatment have to be strictly followed. When greater volumes of HES are applied the coagulation parameters should be closely monitored and the infusion of HES should be stopped at the first sign of a coagulation disorder.
Increased mortality in septic and critically ill patients	Some published studies in patients admitted to the intensive care unit and with a generalized infection of the body have indicated an increased risk of susceptibility to death.	HES must not be given to patients suffering from a generalized infection of the body (sepsis) and to critically ill patients typically admitted to the intensive care unit. All requirements as regards indication, contraindications, dosage and duration of treatment have to be strictly followed.
Fluid overload (hyperhydration) and fluid retention (oedema) due to water/sodium overload may occur, in particular in patients with conditions associated with sodium retention (e.g. hypertension, congestive heart failure, peripheral or pulmonary	When fluids are infused to the circulatory system without a proven need for additional fluid volume this might lead to an over-infusion. This in turn might cause the development of oedema where fluid is shifted outside the veins when the body is not able to eliminate the excess fluid in a timely manner or it might be associated with cardiac problems especially in predisposed patients. This risk is aggravated under conditions where the excretion of salts such as sodium chloride is impaired.	All requirements as regards indication, contraindications, dosage and duration of treatment have to be strictly followed. HES is only to be given under conditions of an acute blood loss when the remaining blood volume is not sufficient to maintain normal circulatiory parameters.

Risk	What is known	Preventability
oedema, impaired renal function)		
Use of pharmaceutical drugs for an unapproved indication or in an unapproved age group, unapproved dosage, or unapproved form of administration (Off-label use)	Like all medicinal products HES might be associated with worse outcome or adverse effects when not used according to the specifications as given by the manufacturer in the summary of product characteristics. .	All requirements as regards indication, contraindications, dosage and duration of treatment have to be strictly followed.
Liver injury (hepatic failure)	Some published studies especially in patients admitted to the intensive care unit or with a generalized infection of the body have indicated an increased risk of liver injury.	HES is contraindicated in patients suffering from severely impaired liver function. All requirements as regards indication, contraindications, dosage and duration of treatment have to be strictly followed.
Severe haemodilution due to high doses of HES	Infusion of volume replacement solutions such as HES will add additional fluid to the circulatory system thus diluting the blood. Especially under conditions of acute blood loss high doses of HES may lead to an imbalance between the additional fluid volume and the remaining blood components making it necessary to substitute blood components e.g by blood transfusion or by transfusion of specific blood components.	To prevent for a severe haemodiluion caused by high doses of HES all requirements as regards indication, contraindications, dosage and duration of treatment have to be strictly followed.
Itching (Long lasting pruritus)	Itching is uncommon but may occur after treatment, even some weeks after the treatment is stopped. The itching can persist for several months.	Do not use HES in case you are allergic to any of the active substances or any of the other ingredients of this medicine.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Wrong diagnosis of pancreatitis due to elevated serum amylase levels	An inflammation of the pancreas might be falsely diagnosed as specific enzymatic markers for this condition in the blood serum might be transiently elevated after infusion of HES. This increase is considered to be due to the formation of a complex of HES with this marker leading to a transient accumulation in the serum. delayed renal and extrarenal elimination.
Increased mortality in burn patients	Amongst other symptoms early burn injury is characterised by a massive generalized inflammation of the body similar to the symptoms observed in patients suffering from a generalized infection of the body (sepsis). Based on the similarities as regards the pathophysiological mechanisms between these two patient groups the risk of increased mortality as seen in septic patients after infusion of HES might also apply in burn patients. Therefore HES must not be used in burn patients.

Missing information

Risk	What is known
Long-term data in surgical (particularly preoperative) and trauma patients	Insuffient long-term data on surgical/trauma patients are available as regards an increased risk for mortality or an increased need for renal replacement therapy associated with HES therapy.
Use in paediatric population	There is only limited experience of the use of HES 130 in children. Therefore it is not recommended to use HES 130 in children. There is no experience of the use of HES 200 in children. Therefore the use of HES 200 is contraindicated in children.
Use in pregnancy	Harmful effects on the unborn child might occur with HES when you have an allergic reaction to the product. Therefore a pregnant patient will receive this medicine only if the doctor has considered the potential benefits outweigh the possible risks to the unborn child, especially in the first trimester of pregnancy.
Use in Lactation (Excretion of HES in human breast milk)	It is not known whether HES passes into the breast milk. Therefore a physician will administer this solution only if he/she thinks it is necessary and a decision will be made whether to temporarily discontinue breast-feeding.
Use in patients with hepatic impairment	Data with regard the use of HES in patients with severe hepatic impairment are limited. Therefore HES is contraindicated in these patients.
Impact of tissue storage in organs other than the skin, kidney and liver	There is no information available on whether HES is stored in other organs than skin, kidney and liver. Also there is no information availabe on any risk a storage outside the afore mentioned organs migt have.

VI.2.5 Summary of additional risk minimisation measures by safety concern

The additional risk minimisation activities are for the following risks:

Renal injury (need for RRT up to 90 days after HES administration)
Risk minimisation measure: 1) Direct Healthcare Professional Communication
Objective and rationale
• To inform healthcare professionals about the new restriction of use of hydroxyethyl starch containing products
Increased bleeding in patients with coagulation disorders, severely impaired hepatic function, intracranial or cerebral haemorrhage, and open heart surgery in association with cardiopulmonary bypass
Risk minimisation measure: 1) Direct Healthcare Professional Communication
Objective and rationale
• To inform healthcare professionals about the new restriction of use of hydroxyethyl starch containing products
Increased mortality in septic and critically ill patients
Risk minimisation measure: 1) Direct Healthcare Professional Communication
Objective and rationale

• To inform healthcare professionals about the new restriction of use of hydroxyethyl starch containing products
Fluid overload (hyperhydration) and oedema due to water/sodium overload may occur, in particular in patients with conditions associated with sodium retention (e.g. hypertension, congestive heart failure, peripheral or pulmonary oedema, impaired renal function)
Risk minimisation measure: 1) Direct Healthcare Professional Communication
Objective and rationale
• To inform healthcare professionals about the new restriction of use of hydroxyethyl starch containing products
Off-label use
Risk minimisation measure: 1) Direct Healthcare Professional Communication
Objective and rationale
• To inform healthcare professionals about the new restriction of use of hydroxyethyl starch containing products
Hepatic injury
Risk minimisation measure: 1) Direct Healthcare Professional Communication
Objective and rationale
• To inform healthcare professionals about the new restriction of use of hydroxyethyl starch containing products
Severe haemodilution (due to high doses of HES)
Risk minimisation measure: 1) Direct Healthcare Professional Communication
Objective and rationale
• To inform healthcare professionals about the new restriction of use of hydroxyethyl starch containing products
Increased mortality in burn patients
Risk minimisation measure: 1) Direct Healthcare Professional Communication
Objective and rationale
• To inform healthcare professionals about the new restriction of use of hydroxyethyl starch containing products
Long-term data in surgical (particularly perioperative) and trauma patients
Risk minimisation measure: 1) Direct Healthcare Professional Communication
Objective and rationale
• To inform healthcare professionals about the new restriction of use of hydroxyethyl starch containing products
Use in patients with hepatic impairment
Risk minimisation measure: 1) Direct Healthcare Professional Communication
Objective and rationale
• To inform healthcare professionals about the new restriction of use of hydroxyethyl starch containing products

VI.2.6 Planned post authorisation development plan

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Multinational drug utilization study (non-interventional) Category 1	To assess the adherence of the hospital physicians to the revised European Product Information (PI)/Summary of Product Characteristics (SmPC)/Package Leaflet for Hydroxyethyl Starch (HES)-containing medicinal products	not applicable	Planned - Protocol version 1.3_04 February 2015 submitted to PRAC under Article 107n-q procedure according to Directive 2001/83/EC on February 6th 2015.	Planned – Final report will be submitted to PRAC within 24 months of the final protocol approval by PRAC
Multinational randomized clinical trial – phase IV (6% HES 130/0.4 in isotonic electrolyte solution vs. crystalloid solution in elective abdominal surgery) – still under discussion within Scientific Advice procedure EMEA/H/SA/2764/1/2014/II Category 1	still under discussion	still under discussion	Planned, protocol to be submitted to NCAs	Planned – Final report will be submitted to NCAs according to set timelines after Scientific Advice procedure EMEA/H/SA/2764/1/2014/II is finalised
Multinational randomized clinical trial – phase IV (6% HES 130/0.4 in saline vs. crystalloid solution in trauma patients) – still under discussion within Scientific	still under discussion	still under discussion	Planned, protocol to be submitted to NCAs	Planned – Final report will be submitted to NCAs according to set timelines after Scientific Advice procedure EMEA/H/SA/2764/1/2014/II is finalised

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Advice procedure EMEA/H/SA/2764/1/2014/II Category 1				

Studies which are a condition of the marketing authorisation

The above three studies are conditions to the Marketing Authorization Holders of HES containing plasma volume replacement products following Article referrals EMA/H/A-31/1348 and EMA/H/A-107i/1376.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable