Summary of the risk management plan for

Voluven 60mg/ml

(hydroxyethyl starch (HES) 130/0.4)

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This is a summary of the risk management plan (RMP) for Voluven 6%/Voluven Fresenius 6%. The RMP details important risks for use of Voluven 6%/Voluven Fresenius 6%, how these risks can be minimised, and how more information will be obtained about Voluven 6%/Voluven Fresenius 6%'s risks and uncertainties (missing information).

Voluven 6%/Voluven Fresenius 6%'s reference safety information (summary of product characteristics (SmPC), package information leaflet (PIL)) includes essential information for healthcare professionals and patients on how Voluven 6%/Voluven Fresenius 6% should be used.

Important new concerns or changes to the current ones will be included in updates of Voluven 6%/Voluven Fresenius 6%'s RMP.

I. The medicine and what it is used for

Voluven 6%/Voluven Fresenius 6% is authorised for treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient (please refer to PIL for the full indication). It contains hydroxyethyl starch (HES) 130/0.4 as the active substance and it is given intravenously by infusion.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Voluven 6%/Voluven Fresenius 6%, together with measures to minimise such risks and the proposed studies for learning more about Voluven 6%/Voluven Fresenius 6%'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package information leaflet addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Voluven 6%/Voluven Fresenius 6% these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Voluven 6%/Voluven Fresenius 6% is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Voluven 6%/Voluven Fresenius 6% are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Voluven 6%/Voluven Fresenius 6%. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	· Renal injury (need for renal replacement therapy up to 90 days after HES administration) including delayed graft function in organ transplant patients · Increased mortality in septic and critically ill patients as well as patients with burns · Increased bleeding in patients with coagulation disorders, severely impaired hepatic function, intracranial or cerebral haemorrhage and open heart surgery in association with cardiopulmonary bypass · Off-label-use
Important potential risk	· None
Missing information	· Long-term data in surgical (particularly perioperative) and trauma patients · Use in pregnancy and lactation

II.B Summary of important risks and missing information

Important identified risks

Renal injury (need for renal replacement therapy up to 90 days after HES administration) including delayed graft function in organ transplant patients	
Evidence for linking the risk to the medicine	Renal injury requiring renal replacement therapy is a serious adverse reaction that may result in persistent or significant disability or incapacity and may have a fatal outcome. The severity of delayed graft function in organ transplant patients ranges from delayed graft function up to irreversible graft failure.
Risk factors and risk groups	Patients with renal impairment or renal replacement therapy/septic patients/critically ill patients/organ transplant patients. Additional risk factors are overdose/long-term use.
Risk minimisation measures	Routine risk minimisation measures:

Renal injury (need for renal replacement therapy up to 90 days after HES administration) including delayed graft function in organ transplant patients	
	Summary of product characteristics (SmPC)/package information leaflet (PIL) sections · Black box warning at the top of the SmPC/PIL as well as warning on the outer and immediate packaging ("Do not use in sepsis, renal impairment, or critically ill patients. See all contraindications in the SmPC") · Posology and method of administration · Contraindications · Special warnings and precautions for use (including advice regarding monitoring of renal function for at least 90 days) · Undesirable effects Legal status: Medical prescription required <u>Additional risk minimisation measures:</u> · Direct healthcare professional communication (DHPC) · Controlled access programme · Training material
Additional pharmacovigilance activities	· Two randomised, controlled phase IV studies, one in surgery and one in trauma patients · Drug Utilisation Study (DUS) to assess the effectiveness of the new additional measures Please refer to section II.C of this summary for an overview of the post-authorisation development plan.

Increased mortality in septic and critically ill patients as well as patients with burns	
Evidence for linking the risk to the medicine	Use of HES in this population may result in death.
Risk factors and risk groups	Patients with renal impairment or renal replacement therapy/septic patients/critically ill patients/patients with burns.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC/PIL sections · Black box warning at the top of the SmPC/ PIL as well as warning on the outer and immediate packaging ("Do not use in sepsis, renal impairment, or critically ill patients. See all contraindications in the SmPC") · Contraindications Legal status: Medical prescription required <u>Additional risk minimisation measures:</u> · DHPC · Controlled access programme

Increased mortality in septic and critically ill patients as well as patients with burns	
	· Training material
Additional pharmacovigilance activities	DUS to assess the effectiveness of the new additional measures Please refer to section II.C of this summary for an overview of the post-authorisation development plan.

Increased bleeding in patients with coagulation disorders, severely impaired hepatic function, intracranial or cerebral haemorrhage and open heart surgery in association with cardiopulmonary bypass	
Evidence for linking the risk to the medicine	Increased bleeding in vulnerable patients is a serious adverse reaction that may be life-threatening and may result in death.
Risk factors and risk groups	Patients with intracranial or cerebral haemorrhage, severe coagulopathy, severely impaired hepatic function or undergoing open heart surgery.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC/PIL sections · Contraindications · Special warnings and precautions for use (including advice regarding monitoring of blood coagulation parameters) Legal status: Medical prescription required <u>Additional risk minimisation measures:</u> · DHPC · Controlled access programme · Training material
Additional pharmacovigilance activities	DUS to assess the effectiveness of the new additional measures Please refer to section II.C of this summary for an overview of the post-authorisation development plan.

Off-label use	
Evidence for linking the risk to the medicine	Use of HES in situations not in accordance with the authorised product information (e.g. contraindications) may lead to serious potentially fatal outcomes.
Risk factors and risk groups	All patients groups.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC/PIL sections · Contraindications

Off-label use	
	· Special warnings and precautions for use Legal status: Medical prescription required Additional risk minimisation measures: · DHPC · Controlled access programme · Training material
Additional pharmacovigilance activities	DUS to assess the effectiveness of the new additional measures Please refer to section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risks

None

Missing information

Long-term data in surgical (particularly perioperative) and trauma patients	
Risk minimisation measures	Routine risk minimisation measures: SmPC/PIL sections · Special warnings and precautions for use Legal status: Medical prescription required Additional risk minimisation measures: · Controlled access programme
Additional pharmacovigilance activities	Two randomised, controlled phase IV studies, one in surgery and one in trauma patients. Please refer to section II.C of this summary for an overview of the post-authorisation development plan.

Use in pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures: SmC/PIL sections · Fertility, pregnancy and lactation Legal status: Medical prescription required Additional risk minimisation measures: · Controlled access programme

II.C Post-authorisation development plan

II.C.1 Studies which are conditions to the marketing authorisations

The following studies are conditions of the marketing authorisation:

Ongoing studies:

- Prospective, randomised, controlled, double-blind, multi-centre, multinational study on the safety and efficacy of a 6% Hydroxyethyl starch (HES) sOlution versus an Electrolyte solutioN In patients undergoing eleCtive abdominal Surgery (PHOENICS)

  Purpose of the study:

  Investigation of the safety and efficacy of a 6% hydroxyethyl starch solution (HES 130) versus a balanced crystalloid solution in patients undergoing major elective abdominal surgery

  Study status: ongoing

  Sponsor: B.Braun Melsungen

  Collaborator: Fresenius Kabi Deutschland GmbH

- PragmaTic, prospEctive, randomised, controlled, double-blind, mulTi-centre, multinational study on the safety and efficacy of a 6% HydroxYethyl Starch (HES) solution versus an electrolyte solution in trauma patients (TETHYS)

  Purpose of the study:

  Investigation of the safety and efficacy of a 6% hydroxyethyl starch solution (HES 130) versus a balanced crystalloid solution in trauma patients

  Study status: ongoing

  Sponsor: B.Braun Melsungen

  Collaborator: Fresenius Kabi Deutschland GmbH

Planned study:

- Drug Utilisation Study

  Purpose of the study:

  Assessment of the effectiveness of the new measures requested

  Study status: planned

  Sponsor: Fresenius Kabi Deutschland GmbH

  Planned Collaborator: B.Braun Melsungen

II.C.2 Other studies in post-authorisation development plan

There are no other on-going and planned studies for Voluven 6%/Voluven Fresenius 6% in the EEA.