Voluven 6% balanced, Infusionslösung

[Hydroxyethyl starch (HES) 130/0.4]

Marketing authorisation holder:	Fresenius Kabi (Schweiz) AG Am Mattenhof 4 6010 Kriens
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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Voluven 6% balanced, Infusionslösung is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Voluven 6% balanced, Infusionslösung in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Fresenius Kabi (Schweiz) AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Voluven 6% balanced, Infusionslösung.

Part VI: Summary of the risk management plan

Summary of risk management plan for Voluven 6% balanced, Infusionslösung (hydroxyethyl starch (HES) 130/0.4)

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

Voluven 6% balanced, Infusionslösung'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% balanced, Infusionslösung should be used.

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

I. The medicine and what it is used for

Voluven 6% balanced, Infusionslösung 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% balanced, Infusionslösung, together with measures to minimise such risks and the proposed studies for learning more about Voluven 6% balanced, Infusionslösung'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% balanced, Infusionslösung, 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% balanced, Infusionslösung 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% balanced, Infusionslösung 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% balanced, Infusionslösung. 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 risks	• None
Missing information	• 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	<u>Routine risk minimisation measures:</u> Summary of product characteristics (SmPC)/package information leaflet (PIL) sections

Renal injury (need for renal replacement therapy up to 90 days after HES administration) including delayed graft function in organ transplant patients	
	• 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 studies, one in surgery and one in trauma patients • Joint DUS II to assess the effectiveness of the implemented 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 • Training material

Increased mortality in septic and critically ill patients as well as patients with burns	
Additional pharmacovigilance activities	• Joint DUS II to assess the effectiveness of the implemented 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	• Joint DUS II to assess the effectiveness of the implemented 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 patient 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 <u>Additional risk minimisation measures:</u> • DHPC • Controlled access programme • Training material
Additional pharmacovigilance activities	• Joint DUS II to assess the effectiveness of the implemented 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

Use in pregnancy and lactation	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmC/PIL sections • Fertility, pregnancy and lactation. Deletion of the paragraph related to use during Caesarean section Legal status: Medical prescription required <u>Additional risk minimisation measures:</u> • 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 study (at DLP):

- **P**rospective, randomised, controlled, double-blind, multi-centre, multinational study on the safety and efficacy of a 6% **H**ydroxyethyl starch (HES) s**O**lution versus an **E**lectrolyte solutio**N** **I**n patients undergoing ele**C**tive abdominal **S**urgery (**PHOENICS)**

  <u>Purpose of the study:</u>

  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 at DLP. The formal end of the study (last 90-day follow-up visit as defined in the protocol) was achieved in July, 2022. The clinical study report is finalised. However, data collection regarding the 1-year follow up phone calls is continuing, and the data base lock for the 1-year follow up data is planned for June 2023.

Sponsor[1]: Fresenius Kabi Deutschland GmbH

Collaborator: B. Braun Melsungen

Completed studies:

- Pragma**T**ic, prosp**E**ctive, randomised, controlled, double-blind, mul**T**i-centre, multinational study on the safety and efficacy of a 6% **H**ydroxYethyl **S**tarch (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: Completed. The formal end of the study (last 90-day follow-up visit as defined in the protocol) was achieved in July, 2022. The clinical study report is finalised.

  Sponsor[2]: Fresenius Kabi Deutschland GmbH

  Collaborator: B.Braun Melsungen

- Drug Utilisation Study I

  Purpose of the study:

  Assessment of the effectiveness of the measures following the CMDh position dated October 2013

  Study status: Completed

  Sponsor: Fresenius Kabi Deutschland GmbH

- Drug Utilisation Study II

  Purpose of the study:

  Assessment of the effectiveness of the measures following CMDh position dated June 2018

  Study status: Completed

  Sponsor: Fresenius Kabi Deutschland GmbH

  Collaborator: B. Braun Melsungen

Planned study:

There is currently no study planned in the EU.

[1] B. Braun acted as initial sponsor and Fresenius Kabi as collaborator. In 2019 both MAHs decided to transfer the sponsorship. Fresenius Kabi became the formal study sponsor in all participating countries of the PHOENICS and the TETHYS study.

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

There are no other on-going and planned studies for the product in the EEA.