Rapporteur’s Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended

Voluven Fresenius 6 % Infusionslösung
Poly (O-2-hydroxyethyl) starch

DE/W/048/pdWS/001

Marketing Authorisation Holder:
Fresenius Kabi Deutschland GmbH

<table>
<thead>
<tr>
<th>Rapporteur:</th>
<th>Germany (DE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finalisation procedure:</td>
<td>17.10.2012</td>
</tr>
<tr>
<td>Date of finalisation of PAR:</td>
<td>23.11.2012</td>
</tr>
</tbody>
</table>
**ADMINISTRATIVE INFORMATION**

| **Invented name of the medicinal product:** | Voluven Fresenius 6 % Infusionslosung |
| **INN (or common name) of the active substance(s):** | Poly (O-2- hydroxyethyl) starch |
| **MAH:** | Fresenius Kabi Deutschland GmbH |
| **Currently approved Indication(s):** | Therapy and prophylaxis of hypovolaemia. |
| **Pharmaco-therapeutic group (ATC Code):** | B05A A07 |
| **Pharmaceutical form(s) and strength(s):** | Solution for infusion 60 mg/mL |
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I. EXECUTIVE SUMMARY

The MAH proposes changes to the SmPC and PL changes in sections 4.2 and 4.4 in regard of children from 2 years to 12 years of age.

Summary of outcome

☐ No change
☒ Change
   ☒ New study data: Data about efficacy and safety of 6% hydroxyethyl starch 130/0.4 (Voluven®) vs. 5% HSA in volume replacement therapy during elective open-heart surgery in paediatric patients (section 5.1)
   ☒ New safety information: Currently available information for the use in paediatric patients as described in section 5.1 and section 4.4
   ☒ Paediatric information clarified: section 4.2
☐ New indication: <section(s) xxxx, xxxx>

II. RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Rapporteur considers that the worksharing application DE/W/048/pdWS/001 for Voluven Fresenius 6 % Infusionslösung (Poly (O-2- hydroxyethyl) starch) for the amendment of the posology in paediatric patients of 2 to 12 years with the inclusion of additional paediatric data in the SPC is approvable.

III. INTRODUCTION

On 29th November 2011, the MAH submitted a completed paediatric study for Voluven, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided on 21st November 2011.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Voluven and that there is no consequential regulatory action.
The MAH proposed to include the following text is proposed into the Product Information of Voluven:

Section “4.2 Posology and method of administration”:

[...]

Limited Clinical data on the use of Voluven Fresenius in paediatric patients is available. In 41 children including newborns to infants (< 2 years), a mean dose of 16 ± 9 ml/kg was administered safely and well tolerated for stabilisation of haemodynamics (see section 4.4). Furthermore, in 31 children from 2 – 12 years of age a mean dose of 36 ± 11 ml/kg was administered safely and well tolerated for stabilisation of haemodynamics.

The dosage in children should be adapted to the individual patient colloid needs, taking into account basic disease, haemodynamics, and hydration status.”

[...]

Section “4.4 Special warnings and special precautions for use”:

[...]

There is limited experience on the use of Voluven Fresenius in children. In cardiac and non-cardiac surgery of paediatric patients up to 12 years of age, the tolerability of Voluven Fresenius administered perioperatively was comparable to 5% albumin. Voluven Fresenius may be given to premature infants and newborns only after careful risk/benefit evaluation.

IV. SCIENTIFIC DISCUSSION

IV.1 Clinical aspects

1. Introduction

Hydroxyethyl starch (HES) infusion solutions are artificial colloids containing poly (O-2-hydroxyethyl) starch and are well known to the medical community. HES solutions are used as plasma substitutes and in volume replacement therapy worldwide for more than 30 years. Hydroxyethyl starches are eliminated mainly via the kidneys after hydrolysis by plasma amylases. The molecular weight and the degree of substitution at the anhydroglucose residues determines the rate of enzymatic degradation of HES. Voluven 6% was first registered for therapy and prophylaxis of hypovolaemia in Germany since June 1999 and in many other European Union member states since 2000. The products are referred to as hydroxyethyl starch HES 130/0.4 in the AR.

Hydroxyethyl starch is widely used in fluid therapy to increase intravascular volume. Comparing to plasma products it is free of disease transmission risk. In paediatric cardiac surgery it has
limited acceptance because of early reports of abnormal coagulation\textsuperscript{1,2}. However the low molecular weight HES 130/0.4 showed favourable coagulation results\textsuperscript{3}.

2. Clinical study

The clinical development program in support of an Article 46 EU paediatric worksharing procedure application for hydroxyethyl starch 130/0.4 in paediatric patients 2 to 12 years of age consists of one clinical trial:

\textit{Study Code HE06-001-CP4:}
\textit{Efficacy and safety of 6\% hydroxyethyl starch 130/0.4 (Voluven\textsuperscript{®}) vs. 5\% HSA in volume replacement therapy during elective open-heart surgery in paediatric patients.}

- **Methods**

  - **Objective(s)**
    To demonstrate equivalence of 6 \% HES 130/0.4 and HSA 50 g/L with regard to the total volume of colloid solution (HES/HSA plus rescue colloid, if applicable) in mL/kg body weight required for intraoperative volume replacement including priming of the extracorporeal circulation (ECC) device (primary efficacy endpoint).
    Secondary objectives were to compare haemodynamics, fluid input/output, the use of vasoactive and inotropic drugs, and safety parameters such as blood gas analyses, laboratory parameters, haemostasis, urinary biomarkers of acute kidney injury, blood loss and transfusion, patient outcome, and adverse events (AEs).

  - **Study design**
    A multi-centre, randomised, controlled, parallel-group, double-blind trial in paediatric patients, 2 to 12 years of age, undergoing elective open-heart surgery.
    Patients received study drug (HES/HSA) a) as part of the priming of the ECC, depending on the patient’s body weight and the total volume of the ECC, and b) for plasma volume replacement as required in the individual patient and up to the maximum dosage (50 mL/kg body weight/day). Study drug administration could already be started before ECC, but the administration remained limited to the intraoperative period. Once the maximum dose was reached intraoperatively, the rescue colloid (= HSA 50 g/L) for which there is no daily dose limitation was used in both groups, if required.

  - **Study population /Sample size**
    Sixty patients planned in the protocol (30 in each treatment group), 61 patients randomised. One patient received no study drug and was excluded from the safety analyses. Fifty-five patients were included in the per-protocol (PP) population.
    Fifty-two patients completed the study, eight patients completed the treatment and postoperative period but were lost to follow-up (Day 28).

  - **Treatments**

\textsuperscript{3} Langeron O, Doelberg M, Ang ET, Bonnet F, Capdevila X, Coriat P. Voluven, a lower substituted novel hydroxyethyl starch (HES 130/0.4), causes fewer effects on coagulation in major orthopedic surgery than HES 200/0.5. Anesth Analg. 2001;92(4):855-62.
Study drug was dispensed to the investigator(s) by the pharmacy at each site taking into account the body weight of the individual patient and the maximum dosage allowed for the investigational drug (50 mL/kg body weight/day). The administration of study drug was done by the anaesthetist and partly by the perfusionist who filled the ECC bypass machine. A patient received either investigational or control drug intraoperatively:

- **Outcomes/endpoints**
  The primary objective of the study was to demonstrate equivalence of Voluven and HSA with regard to the total volume of colloid solution (Voluven/HSA plus rescue colloid, if applicable) in mL/kg body weight required for intraoperative volume replacement including priming of the ECC.

  Secondary objectives were to compare haemodynamics, fluid input/output, the use of vasoactive and inotropic drugs, and safety parameters such as blood gas analyses, laboratory parameters, haemostasis, urinary biomarkers of acute kidney injury, blood loss and transfusion, patient outcome and AEs.

- **Statistical Methods**
  Data management was performed on the following system: Oracle Clinical® Vs 4.5. Statistical analysis was performed using SAS 9.1.3 in a Unix environment.

  The following populations were distinguished in the analysis:
  - The safety population was defined as all patients who were treated with study medication.
  - The ITT population was defined as all patients who where randomised (receiving a randomisation number).
  - The PP population was defined as all patients in the ITT population, without any major protocol deviation as defined at the BDRM which took place on October 05, 2010.

  Efficacy was summarised for both the ITT population and the PP population. The PP population was considered the primary population for analysis. Safety was summarised for the safety population.

  The primary variable for assessing therapeutic equivalence was defined as the total volume of colloid solution (Voluven/HSA plus rescue colloid, if applicable), in mL/kg body weight required for intraoperative volume replacement including priming of the ECC.

  The aim of the study was to prove equivalence, whereby the investigational drug was considered equivalent to the control drug, if the ratio of means investigational/control (plus any rescue colloid) was in the range 0.55 - 1.82. Assuming a coefficient of variation of 0.363 and a desired power of 90 % with a type I level of 2.5 %, N=11 patients per treatment group were needed. The power was calculated by means of the software SAS, version 9.1.3, PROC POWER. Nevertheless, more patients were required for the assessment of safety, therefore 2 × 30 patients were planned to be included in this study with a comparable enrolment in both centres.

#### Results

- **Recruitment/ Number analysed**
  A total of 61 patients were randomised to Voluven (N = 31) or HSA (N=30). One patient in the HSA group (patient 1-39) was randomised in error and was not treated with study medication due to aspirin intake within 14 days prior to the surgery. For this patient no
data on the completion of the study were available. From the remaining 60 patients who were treated with study medication, 52 patients completed the study and 8 patients withdrew prematurely due to protocol violations. All patients who were reported with protocol violations as reason of premature withdrawal were lost to follow-up (only partial information could be obtained at the follow-up assessment). Patients were enrolled in two centres. In Brussels, 60 patients were screened, 40 patients were randomised and 39 patients were treated. In Linz, 39 patients were screened and 21 patients were randomised and treated.

The ITT population comprised all 61 randomised patients, one patient (no. 1-39) was excluded, and therefore, the safety population comprised 60 patients only. Six patients, 2 patients (6.5 %) in the Voluven group and 4 patients (13.3 %) in the HSA group, had major protocol deviations and were excluded from the PP population which comprised 55 patients, 29 (93.5 %) in the Voluven group and 26 (86.7 %) in the HSA group.

- **Baseline data**
  Demographic data for the ITT population are shown below:
### Table 2: Demographic data (ITT population)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Voluven (N=31)</th>
<th>HSA (N=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>Mean</td>
<td>5.2</td>
<td>4.0</td>
</tr>
<tr>
<td>Range</td>
<td>2 - 12</td>
<td>2 - 9</td>
</tr>
<tr>
<td>Ethnic origin (n (%))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian/White</td>
<td>19 (61.3)</td>
<td>16 (53.3)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (35.5)</td>
<td>13 (43.3)</td>
</tr>
<tr>
<td>Black</td>
<td>0 (0.0)</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>Oriental/Asian</td>
<td>1 (3.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Sex (n (%))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15 (48.4)</td>
<td>17 (56.7)</td>
</tr>
<tr>
<td>Female</td>
<td>16 (51.6)</td>
<td>13 (43.3)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>Mean</td>
<td>106.6</td>
<td>101.3</td>
</tr>
<tr>
<td>Range</td>
<td>86 - 153</td>
<td>78 - 130</td>
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<tr>
<td>Weight (kg)</td>
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<td></td>
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<tr>
<td>N</td>
<td>31</td>
<td>30</td>
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<tr>
<td>Mean</td>
<td>18.2</td>
<td>15.4</td>
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<tr>
<td>Range</td>
<td>9 - 55</td>
<td>8 - 28</td>
</tr>
<tr>
<td>Weight category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 12 kg</td>
<td>25 (80.6)</td>
<td>26 (86.7)</td>
</tr>
<tr>
<td>≤ 12 kg</td>
<td>6 (19.4)</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>Mean</td>
<td>15.3</td>
<td>14.8</td>
</tr>
<tr>
<td>Range</td>
<td>12 - 23</td>
<td>12 - 19</td>
</tr>
</tbody>
</table>
Efficacy results
The primary efficacy endpoint was the total volume of colloid solution (Voluven/HSA plus rescue colloid, if applicable) in mL/kg body weight required for intraoperative volume replacement therapy including priming of the ECC. In the PP population, the mean volume of colloid solution required intraoperatively was 36.60 mL/kg body weight (SD = 11.76) in the Voluven group and 36.97 mL/kg body weight (SD = 11.86) in the HSA group. The confidence interval for the ratio of means was within the predefined equivalence range of [0.55; 1.82] for the PP population.

For the PP population the mean total volume of study drug intraoperatively was 35.99 mL/kg BW in the HES 130/0.4 group and 36.11 mL/kg BW in the Albumin group. The volume of rescue colloid was interpolated. Three patients in the HES 130/0.4 group received a mean volume of 5.86 mL/kg BW and 5 patients in the Albumin group received a mean volume of 4.46 mL/kg BW.

The results for the total volume of study drug were similar in the ITT population. However, 4 patients in the HES 130/0.4 group received a mean volume of rescue colloid...
of 4.73 mL/kg BW and 8 patients in the Albumin group received a mean volume of 11.44 mL/kg BW.

According to the secondary endpoints the mean total fluid input (overall time) in mL/kg body weight was similar between treatment groups (Voluven: 246.76 mL/kg body weight, HSA: 248.20 mL/kg body weight, PP population). Total fluid output (overall time) in mL/kg body weight was not considerably different between both treatment groups (Voluven: 195.48 mL/kg body weight, HSA: 181.13 mL/kg body weight; PP population) as supported also by the results for the intention-to-treat (ITT) population.

In the mean, fluid balance was more positive for HSA, in particular for the intraoperative period until arrival on ICU (15.38 mL/kg body weight for Voluven versus 27.66 mL/kg body weight for HSA; PP population) in both analyses populations. The course of haemodynamics during the study (baseline – 2nd postoperative morning) was comparable between the two treatment groups. Furthermore, no notable differences were detected for the use of vasoactive and inotropic drugs.

- **Safety results**
  A comparison of AEs on the level of System Organ Classes (SOCs) is shown in the table below:
AEs with an at least possible relationship to study drug were reported for 17 patients (54.8%) in the HES 130/0.4 group and 8 patients (27.6%) in the Albumin group (Table 4). This proportion between the treatment groups was influenced by the incidence of hypoproteinaemia [which was reported as an AE for 10 (32.3%) patients in the HES 130/0.4 group only] in the HES 130/0.4 group. The AE hypoproteinaemia was an expected result since hypoproteinaemia is a consequence of the desired haemodilution achieved with HES 130/0.4 whereas the administration of Albumin prevents a decrease of protein levels by nature. Table 4 also gives an overview of AEs after exclusion of hypoproteinaemia as an expected AE in the HES 130/0.4 group.

AEs with a potential relationship to study procedure were reported for 9 patients (29.0%) in the HES 130/0.4 group and 6 patients (20.7%) in the Albumin group (Table 4).
The maximal severity grade of AEs was 4 (very severe) which occurred in 7 patients (22.6%) in the HES 130/0.4 group and 4 patients (13.8%) in the Albumin group (Table 4). 11 patients (35.5%) in the HES 130/0.4 group and 7 patients (24.1%) in the Albumin group had SAEs (Table 4). Importantly, none of the SAEs was evaluated as related to study medication. Overall, the incidence was low and the distribution of SAEs revealed no disadvantage for any of the two treatment groups. In 2 patients in the Albumin group only, renal replacement therapy was required in the course of SAEs. All patients recovered except for one patient of the HES 130/0.4 group and 2 patients of the Albumin group who recovered with sequelae. Two SAEs of the Albumin group were ongoing at the time of database closure. One was assessed as (outcome) unknown and one as persistent. For more details on SAEs please refer to Section 12.3.2 of the CSR. No patient died in this study and no AE was leading to dose reduction or discontinuation of study drug.

### Table 4

**Overview of Adverse Events (Safety Population)**

<table>
<thead>
<tr>
<th></th>
<th>All AEs</th>
<th>AEs excluding Hypoprothrombinaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HES 130/0.4</td>
<td>Albumin (N=29)</td>
</tr>
<tr>
<td></td>
<td>(N=31)</td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Any AE</td>
<td>30 (96.8)</td>
<td>29 (100.0)</td>
</tr>
<tr>
<td>Any serious AE</td>
<td>11 (35.5)</td>
<td>7 (24.1)</td>
</tr>
<tr>
<td>Any AE with maximal grade 5 (death)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Any AE with maximal grade 4 (very severe)</td>
<td>7 (22.6)</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>Any AE with maximal grade 3 (severe)</td>
<td>19 (61.3)</td>
<td>13 (44.8)</td>
</tr>
<tr>
<td>Any AE leading to discontinuation of study drug</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Any AE related to study drug</td>
<td>17 (54.8)</td>
<td>8 (27.6)</td>
</tr>
<tr>
<td>Any AE related to study procedure</td>
<td>9 (29.0)</td>
<td>6 (20.7)</td>
</tr>
</tbody>
</table>

No patient died in this study.

For blood gases and parameters of haematology and clinical chemistry no relevant differences were found between treatment groups with regard to changes in the course of the study. However, an effect of the treatment was seen for total protein since mean/median values after surgery were decreased in the Voluven group only. Furthermore, for parameters of haemostasis the ANCOVA analyses revealed no significant difference between the two treatment groups. Renal biomarkers were increased in all patients after surgery and dropped again during the postoperative period. There was no relevant difference between the treatment groups. Since there were only single cases with renal dysfunction and/or a relevant increase in serum creatinine in this study population, no conclusions can be drawn on
the suitability of any of the renal biomarkers to indicate a relevant deterioration in renal function. Calculated perioperative red blood cell loss was similar between the treatment groups. The ratio of means of perioperative blood cell loss μVoluven/μHSA was estimated as 0.94 with a 95% confidence interval of (0.66, 1.33). The mean total volume of transfused blood products was almost comparable between the treatment groups. Transfusion of red blood cells affected less than 50% of the patients in the Voluven group. No relevant differences for median values were found for outcome parameters such as duration of ECC and surgery, duration of mechanical ventilation, and the mean length of stay in ICU.

3. Discussion on clinical aspects

A clinical phase IV study conducted for this particular Article 46 EU paediatric worksharing procedure application has been performed and submitted in which 31 paediatric patients were treated with HES 130/0.4 and 29 patients with 5% HAS in an open heart surgery setting.

The design of the study has been considered acceptable to prove equivalence of HES 130/0.4 with 5% human serum albumin, the so called “golden standard” in paediatric open heart surgery, especially for priming of the extracorporal circuit (EOC).

The new data obtained by this clinical study should be added to the Product Information.

The results of the study HE06-001-CP4 demonstrated equivalence of HES 130/0.4 in volume replacement therapy in paediatric patients 2 to 12 years of with 5% HSA, the standard volume expander in this age group. Even that this study was conducted in a cardiac surgery setting with perioperative fluid therapy, the results can be assigned to other types of paediatric surgeries. The safety analyses of the study revealed no relevant or unexpected differences between the two treatment groups and proved the overall safety profile of Voluven to be similar to that of 5% HSA.

In respect of the proposed text RMS and CMS noted some modifications.

In the submitted paediatric study admission of the study drug was limited to 50 mL/Kg body weight/day and should be mentioned in the proposed text as also reference should be made according to the limited data of long-term use of HES 130/0.4 in children.

According to the limited study population in an open heart surgery setting revisions of the proposed text in the SmPC in section 4.2 and an amendment in section 5.1 were requested.

The requests for the proposed text for children were as follows:

### Section 4.2 Posology

**Paediatric population**

Limited Clinical data on the long-term use in children is available for Voluven Fresenius. In newborns to infants (< 2 years), a mean dose of 16 ± 9 ml/kg and in children from 2 – 12 years of age a mean dose of 36 ± 11 ml/kg was administered safely and well tolerated. The dosage in children should be adapted to the individual patient colloid needs, taking into account basic disease, haemodynamics, and hydration status and should not exceed the
maximum dosage of 50 ml/kg body weight/day. Currently available information is described in section 5.1.

There was also an agreement that the fact of the limited study population in an open heart surgery setting must be mentioned in the new wording. According to A GUIDELINE ON SUMMARY OF PRODUCT CHARACTERISTICS of September 2009 posology recommendations should be given for each of the paediatric subsets and the dose should be expressed according to weight or body surface area. Data on clinical studies should appear in section 5.1 and read as follows:

**Section 5.1 Pharmacodynamic properties**

**Paediatric population**

Clinical data on the use of Voluven Fresenius in paediatric patients is available. In 41 children including newborns to infants (< 2 years), a mean dose of 16 ± 9 ml/kg was administered safely and well tolerated for stabilisation of haemodynamics in non-cardiac perioperative settings. Furthermore, in 31 children from 2 – 12 years of age a mean dose of 36 ± 11 ml/kg was administered safely and well tolerated for stabilisation of haemodynamics during open heart surgery.

In section 4.4 the MAH added the following reference to section 5.1:

**Section 4.4 Special warnings and special precautions for use**

[...]

Voluven Fresenius may be given to premature infants and newborns only after careful risk/benefit evaluation. Currently available information for the use in paediatric patients is described in section 5.1.

[...]

The Applicant accepted all the changes as requested. The text in the respective sections of the SmPC has been revised.

The reference made in section 4.4 in accordance to the paediatric information in section 5.1 was accepted by RMS and CMSs.

**V. RAPPORTEUR’S OVERALL CONCLUSION AND RECOMMENDATION**

➢ **Overall conclusion**

The results from the submitted clinical study (Study Code HE06-001-CP4) allow changes to the SmPC regarding the use of Voluven in children. The Applicant has addressed these changes in the clinical overview and supported them with clinical relevant data.

The Applicant accepted the requested text modifications and amendments due to the fact that the new gained information provided by the Applicant is limited to perioperative fluid therapy, especially for the priming of the cardiopulmonary bypass.
The use of 6% HES 130/0.4 in paediatric patients of 2 to 12 years of age is supported and the worksharing application DE/W/048/pdWS/001 is approvable.

➢ **Recommendation**

A Type IB variation 60 days after finalisation of the worksharing procedure should be submitted in order to update the product information.

VI. **LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED**

Name of the medicinal product: Voluven Fresenius 6 % Infusionslösung
Active substance: Poly(O-2- hydroxyethyl) starch
Marketing Authorisation Holder: Fresenius Kabi Deutschland GmbH