In this submission, 13 literature articles related to the pharmacokinetic aspects of Venofer® and some pharmacokinetic summaries from the referenced articles are provided. Information on the drug formulations that were used for the clinical safety and efficacy studies and the analytical methods used in these studies is also provided (see Attachment I).

Overall, it is considered that the sponsor has provided sufficient information to permit a substantive review of the NDA.

RECOMMENDATION

NDA 21-135 submitted for iron sucrose injection (Venofer®) by the sponsor, Luitpold Pharmaceuticals, Inc. on August 6, 1999 has been reviewed for filing by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics. It is considered that sufficient information has been provided to permit a substantive review and the NDA. Accordingly, the NDA is considered filable.

Please convey this Recommendation, as appropriate, to the sponsor.

Attachment I is retained in the Office of Clinical Pharmacology and Biopharmaceutics and may be obtained upon request.

[Signature] 09/23/99
David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

RD Initialed by David Lee, Ph.D. [Signature] 9/27/99
FT Initialed by David Lee, Ph.D. [Signature] 9/27/99

cc: NDA 21-135, HFD-180, HFD-180 (Strongin), HFD-870 (M. Chen, Hunt, Lee and Udo), CDR (Attn: Barbara Murphy).

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### Attachment B IN VIVO STUDY DATA SUMMARY FOR IRON SUCROSE

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Route of Administration</th>
<th>Dose (mg)</th>
<th>Mean Cmax ± SD</th>
<th>Mean Tmax (hr)</th>
<th>Mean Vd ± SD</th>
<th>Mean AUC(0-1) ± SD</th>
<th>Mean Kel (hr⁻¹)</th>
<th>Mean Urinary Excretion (mg) ± SD</th>
<th>Mean CLp (mL/min)</th>
<th>Mean CLr (0-24 hr) ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacDougall J et al (Report. March 5, 1999)</td>
<td>IV</td>
<td>200</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Dangelmann B.G. et al. Internal report. 7.7.1995. Arzneim.- Forsch/Der. Res. 1996; 46(1): 6</td>
<td>IV</td>
<td>100</td>
<td>537.7 ± 106.9 µmol/L (30 mg/L) at 10 min; Cₐ: 361.2 ± 146.9 µmol/L</td>
<td>NR</td>
<td>7.3 ± 2.1L</td>
<td>1491 ± 212 µmol/L/h</td>
<td>NR</td>
<td>5.19 ± 1.28 mg /24 h</td>
<td>NR</td>
<td>1.23 ± 0.22 /h (20.5 ± 3.7 mL/min)</td>
</tr>
<tr>
<td>Beshara S et al (Internal Report. 14.5.1997)</td>
<td>IV</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Major A et al (Report 11.3.1997)</td>
<td>IV</td>
<td>200</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

SD: Standard deviation; NR: not reported; min: minute; mL: milliliter; µmol/L: micromolar; L: liter; mg: milligram; h: hour; IV: intravenous; Cₐ: Initial concentration, AUC: area under the curve.

Cmax: maximum concentration, CLp: total body clearance, CLr: total clearance, Vd: volume of distribution.

**APPEARS THIS WAY ON ORIGINAL**
<table>
<thead>
<tr>
<th>Study Number</th>
<th>Route of Administration</th>
<th>Dose (mg)</th>
<th>Mean Cmax (µg/mL) ± SD</th>
<th>Mean Tmax (hr)</th>
<th>Mean Log Vd (L) ± SD</th>
<th>Mean Log AUC(0-24) (µg·hr/mL) ± SD</th>
<th>Mean Log Kel (hr⁻¹)</th>
<th>Mean Log Urinary Excretion (mg) ± SD</th>
<th>Mean Log CLp (mL/min) ± SD</th>
<th>Mean Log CLR (0-24 hr) ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silverberg DS et al. Amer J Kidney Diseases 1996; 27(2): 234-238.</td>
<td>IV</td>
<td>200</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Anakiev A. and Gekova K. Problems of Hematology and Blood Transfusions, in Medicine and Physiology 1970; 13: 295-298.</td>
<td>IV</td>
<td>500</td>
<td>1398 ± 605 µg/dl. (13.98 µg/L) at 4 hr</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>22.4 mg/24 h</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>700-800</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>33.7 mg/24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Krzysko K. et al. Zbl. Pharm. 1984; 123 Heft(10): 598-599.</td>
<td>IV</td>
<td>50</td>
<td>NR</td>
<td>NR</td>
<td>0.395 ± 0.117 L/kg</td>
<td>24.324 ± 15.644 µg/h/mL.</td>
<td>NR</td>
<td>NR</td>
<td>0.074 ± 0.086 L/h/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>500</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NR: Not reported; min: minute; mL: milliliter; umol/L: micromolar; L: liter; mg: milligram; h: hour; IV: intravenous; C: Initial concentration, AUC: area under the curve, Cmax: maximum concentration, CLp: total body clearance, CLR: total clearance, V: volume of distribution, S: standard deviation.
### 6.3 Tabulated Summaries of Bioavailability and Pharmacokinetic Studies

#### Table 2  
Bioavailability Studies: Release of Iron to Transferrin Iron Pool (200 Mg Iron)

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Study Investigator - Coordinating Center(s)</th>
<th>Design</th>
<th>Number of Subjects, Sex, and Age</th>
<th>Diagnosis and Criteria for Inclusion</th>
<th>Duration of Treatment</th>
<th>Test Product Dosage Regimen Route of Administration</th>
<th>Reference Therapy Dose Regimen Route of Administration</th>
<th>Criteria for Evaluation</th>
<th>Results</th>
<th>Safety</th>
</tr>
</thead>
</table>
Group A=20  
Group B=20  
Group C=20  
  
Group A: Mean age 58 years  
13 males  
7 females  
  
Group B: Mean age 63 years  
12 males  
8 females  
  
Group C: Mean age 50 years  
11 males  
9 females | Dialysis patients with anemia of chronic renal failure; serum ferritin 30-300 µg/L, hemoglobin ≤10 g/dL, no parenteral iron administration during the previous two weeks. C-reactive protein <20 mg with or without r-HuEPO | Single application, observation time 0, 0.5, 1, 2, 4, 6, 8, 12, 18, 24, 36, and 48 hours after the start of infusion and 4, 7, and 14 days after infusion (4 weeks) | Group C: 200 mg Fe in 100 mL of 0.9% saline (iron sucrose as Venofer®) infused IV over 30 minutes  
Group A: 200 mg Fe IV (iron dextran) in 100 mL of 0.9% saline infused over 30 minutes; Group B: 200 mg Fe IV (iron dextran) in 100 mL saline infused over 30 minutes | Hemoglobin, hematocrit, red blood cell count, differential white blood cell count, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, white blood cell count, total iron-binding capacity, transferrin saturation, serum iron, serum ferritin, and total circulating iron. | Different degradation kinetics. Peak transferrin saturation was faster (30-60 min) and higher (>100%) in iron sucrose group (C) than in Group A and B (60-70%). During initial 24 hours, iron sucrose group (C) achieved higher serum iron levels than Group A and B. Group B had less effect on serum ferritin than group A and C. | No adverse events with iron dextran (Group A) and iron sucrose (Group C), but three anaphylactic reactions with iron dextran (Group B). |

N: number, mg: milligram, IV: intravenous.
Table 3  Bioavailability Studies: Effects of Erythropoietin With and Without Iron Sucrose Treatment on Reticulocyte Response

<table>
<thead>
<tr>
<th>Name of Company: Venofer®</th>
<th>Name of Finished Product: Venofer®</th>
<th>Name of Active substance(s): Iron Sucrose</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Study</th>
<th>Co-ordinating Center(s)</th>
<th>Design</th>
<th>Number of Subjects, Sex, and Age</th>
<th>Diagnosis and Criteria for Inclusion</th>
<th>Duration of Treatment</th>
<th>Test Product Dosage</th>
<th>Route of Administration</th>
<th>Reference Therapy Regimen Route of Administration</th>
<th>Criteria for Evaluation</th>
<th>Results</th>
<th>Safety</th>
</tr>
</thead>
</table>

NR: Not reported, N: number, IV: intravenous, kg: kilogram, IU: international units.
Table 4  Human Pharmacokinetic Studies: Pharmacokinetics of a Single 100 Mg Dose of Iron Sucrose

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Subjects, Sex, and Age</th>
<th>Diagnosis and Criteria for Inclusion</th>
<th>Duration of Treatment</th>
<th>Test Product</th>
<th>Criteria for Evaluation</th>
<th>Results</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alt. J Section 6</td>
<td>N=12</td>
<td>Adult healthy subjects</td>
<td>Single application</td>
<td>Iron sucrose (Venofer®) 100 mg iron</td>
<td>Hematological parameters, serum iron, serum transferrin, ferritin, urinary iron and sucrose, AUC, AUMC, MRT, CL, Vdss, Vdmin, and t1/2</td>
<td>There was no statistically significant difference in serum iron levels before and 24 hours after injection.</td>
<td>No adverse reactions reported.</td>
</tr>
<tr>
<td>Arzneim.-Forsch./Drug Res. 1996; 6:615-621.</td>
<td>12 males</td>
<td>3 females</td>
<td>35-50 years</td>
<td>Iron sucrose (Venofer®) 100 mg iron</td>
<td>Hematological parameters, serum iron, serum transferrin, ferritin, urinary iron and sucrose, AUC, AUMC, MRT, CL, Vdss, Vdmin, and t1/2</td>
<td>There was no statistically significant difference in serum iron levels before and 24 hours after injection.</td>
<td>No adverse reactions reported.</td>
</tr>
<tr>
<td>-Danielson BG, Salmanson T, Bexendorf H, Geiser P.</td>
<td>-Department of Medicine, University Hospital, Uppsala, Sweden</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 5: Human Pharmacokinetic Study: Pharmacokinetics of Radiolabeled Iron-Sucrose

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Study</th>
<th>Design</th>
<th>Number of Subjects, Sex, and Age</th>
<th>Diagnosis and Criteria for Inclusion</th>
<th>Duration of Treatment</th>
<th>Test Product Dosage Regimen Route of Administration</th>
<th>Reference Therapy Dose Regimen Route of Administration</th>
<th>Criteria for Evaluation</th>
<th>Results</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Att. 4 Section 6</td>
<td>Zbl. Pharm. 1984; 123 Heft(10): 598-599.</td>
<td>Open, crossover</td>
<td>N=11 Sex=NR Age=NR</td>
<td>Healthy subjects</td>
<td>Single bolus injection</td>
<td>Iron sucrose 2.5 mL (50 mg iron) given intravenously</td>
<td>Hemofer® prolongatum 210 mg oral iron as ferrous fumarate</td>
<td>Pharmacokinetic parameters after IV administration and bioavailability after oral administration</td>
<td>Half-life time of serum iron was 9.31 ± 6.77 hours. Iron was mainly distributed in intracellular space. Plasma clearance of 0.074 dm³/hr/kg</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR: Not reported, ml: milliliter, N: number, mg: milligram, kg: kilogram, h: hour.
### Table 6  
**Human Pharmacokinetic Studies: Red Cell Utilization of Radiolabeled Iron Sucrose**

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Study</th>
<th>Design</th>
<th>Number of Subjects, Sex, and Age</th>
<th>Diagnosis and Criteria for Inclusion</th>
<th>Duration of Treatment</th>
<th>Test Product Dosage</th>
<th>Route of Administration</th>
<th>Criteria for Evaluation</th>
<th>Results</th>
<th>Safety</th>
</tr>
</thead>
</table>
| Att. 5 Section 6 | Internal report. 14.5.1997 - Beshara S, Lundqvist H, Sundin J, et al. - Department of Internal Medicine, University Hospital, Uppsala, Sweden | Open | N=6  
2 males  
4 females  
24-63 years | Patients with iron deficiency anemia, renal anemia, or functional iron deficiency anemia | Single application, observation time was 4 weeks prior to inclusion. | 100 mg iron IV as iron sucrose (Venofer®) \(^{57}Fe^{57}Fe\) radio-labeled | Distribution and incorporation of labeled iron: emission scans performed for \(^{57}Fe\) after 90 min. and at 3, 4, 5, 6, 7, and 8 hours. Determination of utilization and incorporation of iron into the red cells over 4 weeks. | All patients showed a significant increase in serum ferritin and transferrin saturation after 24 hours and 1 week; the maximum radiolabeled iron red cell utilization after 15-28 days ranged from 68-97%. Iron deficiency: 88% and 94%. Renal anemia: 76% and 97%. Functional iron deficiency: 68% and 76% | No adverse events observed. |

---

N: number, ml: milliliter, mg: milligram, IV: intravenous.
Table 7  Human Pharmacokinetic Studies: Serum Iron Levels and Urinary Excretion

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Study</th>
<th>Design</th>
<th>Number of Subjects, Sex, and Age</th>
<th>Diagnosis and Criteria for Inclusion</th>
<th>Duration of Treatment</th>
<th>Test Product Dosage Regimen Route of Administration</th>
<th>Criteria for Evaluation</th>
<th>Results</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>NR</td>
<td>Problems of Hematology and Blood Transfusions, In Medicine and Physiologic. 1970; 13: 295-298 -Anatov A. Gekova K.</td>
<td>Open, non-controlled</td>
<td>N=26 3 males 23 females 16-60 years</td>
<td>Iron deficiency anemia caused by achlorhydria, menorrhagia, miscellaneous, and gastric resection</td>
<td>3 days</td>
<td>500 mg iron IV as iron sucrose diluted in 500 mL saline (N=21) 700-800 mg IV iron as iron sucrose (N=5) Total dose 1500-2000 mg iron</td>
<td>Changes in hematological parameters and urinary estimation of iron</td>
<td>Increase in mean hemoglobin, and red cells during and after treatment. Serum iron levels reached a peak after 4 hours and normalized after 2 days. Mean renal elimination was 4-6% of given iron dose.</td>
<td>Mild headache and nausea 500 mg iron in 7.84% of cases. Headache, vomiting and muscular pain in three of 5 patients (2 infusions each) after they received 700-800 mg iron and transient collapse occurred in one patient.</td>
</tr>
</tbody>
</table>

NR: Not reported, N: number, IV: intravenous, mg: milligram.
6.4 Summary of Bioavailability/Bioequivalence Studies

6.4.1 Bioavailability Studies in Dialysis Patients With Anemia.


In a single-center, randomized, open label, parallel, comparative study, Macdougall et al. (1999) [1] evaluated three iron preparations for their ability to release iron to the transferrin iron pool in dialysis patients with anemia of chronic renal failure. Sixty patients (44 receiving erythropoietin) were randomly assigned to receive a single 30 minute intravenous infusion of 200 mg iron in the form of either iron dextrin (iron polymaltose; n=20), or iron dextran (n=20), or iron sucrose (as Venofer®; n=20). Patients were to be stratified according to whether or not they were receiving EPO therapy; however, 73% of all patients were receiving EPO and, as the results were similar for the two strata, all data for +EPO and –EPO patients were combined within each treatment group.

Blood samples for evaluation of biochemical variables were collected at screening and at intervals after injection as follows.

- At 0, 1/4, 1/2, 1, 2, 4, 6, 8, 12, 18, 24, 36 and 48 hours after injection the following were measured: serum iron, serum total iron binding capacity (TIBC), transferrin saturation, and total circulating iron.

- At 48 hours, and 4, 7, and 14 days after injection the following were measured: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelets, serum ferritin, iron, TIBC, transferrin saturation, and total circulating iron.

- At 14 days after injection the following were measured: serum albumin, alkaline phosphatase, aspartate aminotransferase (AST), and bilirubin.

For all 60 patients, baseline ferritin levels were in the range of 27-310 μg/L (mean 116 μg/L). Figure 1 shows that iron sucrose and iron dextrin both produced faster and higher ferritin levels than did iron dextran. Serum ferritin increased over the first two days following the intravenous boluses of iron sucrose and iron dextrin to a maximum value of 200-250 μg/L at-days 4-7. In contrast, intravenous iron dextran did not increase ferritin levels within the first two days after administration. Maximal ferritin levels after intravenous iron dextran were significantly lower (140 μg/L at day 14) compared to the values achieved after iron sucrose and iron dextrin administration.
Figure 1  Serum Ferritin Levels After Intravenous Administration of 200 Mg of Three Forms of Iron (Mean ± Standard Error)

At the doses used for all three preparations, there was no change in mean serum ferritin between day 7 and 14. This suggests there is no need to wait 14 days after administration of IV iron to check serum ferritin levels.

Table 8 shows that serum iron levels at 30 minutes after administration were significantly higher for iron sucrose compared to iron dextran or iron dextrin.

Table 8  Serum Iron Levels 30 Minutes After IV Administration of Three Different Iron Preparations

<table>
<thead>
<tr>
<th>Form of Iron Delivery (200 Mg Iron)</th>
<th>Iron Sucrose</th>
<th>Iron Dextrin</th>
<th>Iron Dextran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Serum Iron</td>
<td>87±22 μmol/L*</td>
<td>44±15 μmol/L</td>
<td>39±13 μmol/L</td>
</tr>
</tbody>
</table>

* Values are means ± standard errors.

Figure 2 shows that peak serum iron levels were significantly higher and levels remained higher for 24 hours with iron sucrose than with other iron preparations. Serum iron levels were similar for iron dextrin and iron dextran.
Figure 2  Serum Iron Levels on Day 1 and Days 2-14 Following IV Administration of 200 Mg Iron Dextran, Iron Dextrin, and Iron Sucrose in Dialysis Patients (Means ± SE)

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Figure 3 shows that peak percent transferrin saturation was higher in patients receiving iron sucrose than in patients receiving other iron formulations. Transferrin saturation values peaked at 30 minutes-1 hour at >100% with iron sucrose and they gradually fell to baseline values over the next 24 hours. For iron dextran and iron dextrin, transferrin saturation peaked at 1 hours at 60-70% and fell within 24 hours to 40%.

**Figure 3** Transferrin Saturation Levels After Intravenous Administration of Three Forms of Iron

The measurement of iron bound specifically to transferrin in plasma in the presence of circulating iron-containing pharmacological compounds presents considerable difficulties. All routine diagnostic methods for the measurement of transferrin iron are predicted on the assumption that no other iron-containing compounds are present in the circulation. All these methods release iron from transferrin by reducing pH to a greater or lesser extent. Therapeutic iron compounds are all constructed to release iron in a controlled fashion in a neutral aqueous environment. At pH 5 or less they will, to a variable extent, release iron that will then become indistinguishable from iron released from transferrin. Both will be detected by a variety of chromogens.

In the present study, transferrin saturation values following iron sucrose administration transiently appeared to exceed the total iron binding capacity of the plasma. The authors believe that this is a reflection of the methodological problems outlined above and which are common to all diagnostic procedures. The apparent super-saturation is a reflection of the degree to which iron from complexed iron compounds, such as iron sucrose, can be released in acid conditions. This in no way reflects the behavior of the compound in a neutral environment and it is impossible using this method to determine whether iron is released either directly to transferrin or any other ligand in the plasma in vivo. Therefore, these results do not indicate any over-saturation of transferrin.

In summary, the results of this study showed different degradation kinetics between the three iron preparations with iron sucrose releasing iron more readily and yielding higher...
transferrin saturation values than the other two intravenous iron preparations. Iron dextran had less effect on serum ferritin compared with iron dextrin or iron sucrose.

6.4.2 Effects of Iron on Reticulocyte Response to Erythropoietin.


In a randomized, controlled, parallel, comparative study, Major et al (1997) [2] compared the effects on cellular characteristics of reticulocytes of a single dose of IV recombinant human erythropoietin (r-HuEPO) combined with 200 mg iron IV as iron sucrose (Venofer®) to the effects of a single dose of IV r-HuEPO administered without iron sucrose. Fourteen healthy volunteers were randomized to receive either 300-IU/kg r-HuEPO and a simultaneous intravenous injection of 200 mg iron sucrose (Group A) or 300 IU/kg r-HuEPO alone (Group B).

Venous blood samples were collected at 24-hour intervals for 8 days in order to measure the following parameters: erythropoietin levels, absolute reticulocyte count, reticulocyte cell hemoglobin content (CHr), reticulocyte cell volume (MCVr), hemoglobin content of young and old reticulocytes (CHyoungR and CHoldR), reticulocyte hemoglobin (retHb; a measure in picograms (pg) of the hemoglobin [Hb] contained in all reticulocytes), serum ferritin.

The two groups did not differ in circulating erythropoietin level or in the absolute reticulocyte count. The two groups did differ in the remaining measures. Data are presented in Table 9 and Figure 4 (adapted from Major et al [2].

**Table 9**

Reticulocyte Cell Hemoglobin Content (CHr) and Serum Ferritin in Normal Subjects Receiving Erythropoietin Alone ("Control"), and Erythropoietin and Iron Sucrose

<table>
<thead>
<tr>
<th>Time</th>
<th>Control CHr (pg) †</th>
<th>Iron Sucrose CHr (pg) †</th>
<th>Control Serum Ferritin (µg/L) †</th>
<th>Iron Sucrose Serum Ferritin (µg/L) †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>31.8±0.9</td>
<td>32.5±1.3</td>
<td>77±7.3</td>
<td>83.7±62.4</td>
</tr>
<tr>
<td>Day 1</td>
<td>32.1±1.2</td>
<td>33±1.5</td>
<td>72.6±68.3</td>
<td>162.6±61.7*</td>
</tr>
<tr>
<td>Day 2</td>
<td>31.4±0.9</td>
<td>32.6±1.1*</td>
<td>58.7±56.1</td>
<td>162.8±51.9*</td>
</tr>
<tr>
<td>Day 3</td>
<td>31.5±1.5</td>
<td>33.5±1.1*</td>
<td>39.3±40.3</td>
<td>138.7±52.8*</td>
</tr>
<tr>
<td>Day 4</td>
<td>32.8±1.8</td>
<td>35±1.1*</td>
<td>42.8±42</td>
<td>121±32.7*</td>
</tr>
<tr>
<td>Day 5</td>
<td>31±1.2</td>
<td>33.4±1.6*</td>
<td>37.7±37.6</td>
<td>92.7±33.9*</td>
</tr>
<tr>
<td>Day 6</td>
<td>30.6±1.7</td>
<td>32.9±2.1*</td>
<td>43.8±40.6</td>
<td>100.4±40*</td>
</tr>
<tr>
<td>Day 7</td>
<td>30.7±1.7</td>
<td>32.9±1.9*</td>
<td>47.4±50</td>
<td>109.4±46.9*</td>
</tr>
</tbody>
</table>

* Mann-Whitney U-test p<0.05 compared with control.
† Results expressed as mean ± standard deviation.
µg/L: microgram per liter.
Table 9 and Figure 4 show that CHr was significantly higher in the iron sucrose + r-HuEPO patients (Group A) from day 3 onward compared with the r-HuEPO patients (Group B).

In the iron sucrose + r-HuEPO group, the content of hemoglobin of young reticulocytes increased and reached a plateau on day 2 which was significantly higher than that of older reticulocytes. The cell hemoglobin content of old reticulocytes increased from day 3, and reached a peak on day 4; it was significantly higher than seen in young erythrocytes.

The iron sucrose + r-HuEPO group showed an almost 100% increase in serum ferritin level on days 1 and 2 which decreased only slightly to baseline after 6 days, followed by a slight increase until day 8. In contrast, serum ferritin levels decreased following r-HuEPO administration alone to approximately half of the baseline values by day 6, and increased only slightly thereafter.

Although the total number of reticulocytes was not different between groups, the reticulocyte Hb content and retHb [measured in pg of the Hb contained in all reticulocytes] increased with a greater response in Group A compared to Group B who received r-HuEPO alone.
These results suggest that iron sucrose significantly potentiates the hematopoietic response to r-HuEPO in normal subjects when both compounds are administered concomitantly.

6.5 Pharmacokinetic Studies

6.5.1 Pharmacokinetics of 100 mg Iron Sucrose


Danielson et al., 1995 [3] performed an open, single dose pharmacokinetic study in 12 healthy subjects following intravenous administration of a single 100 mg dose of iron as iron sucrose (as Venoferr®). The data obtained were evaluated using non-compartmental (nc) and compartmental (c) pharmacokinetic analysis. Subsequently, a Michaelis and Menten model (MM) was used for calculating iron transport with transferrin. The results of the non-compartmental, compartmental and MM model pharmacokinetic analyses are summarized in Table 10.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Method of Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-Compartmental</td>
</tr>
<tr>
<td>C\text{\text{max}} (C_0) \text{\text{C}} \text{\text{max}}</td>
<td>584</td>
</tr>
<tr>
<td>T\text{\text{1/2d}} \text{T_{\text{1/2d}}}</td>
<td>7.0</td>
</tr>
<tr>
<td>MRT \text{MRT t}</td>
<td>8.2</td>
</tr>
<tr>
<td>AUC \text{AUC}</td>
<td>1680</td>
</tr>
<tr>
<td>Total body clearance \text{Total body clearance}</td>
<td>18.5</td>
</tr>
<tr>
<td>\text{L/min}</td>
<td>(L/min)</td>
</tr>
<tr>
<td>V\text{v} \text{V_v}</td>
<td>3.3</td>
</tr>
<tr>
<td>Vd\text{at} \text{V_d at}</td>
<td>8.4</td>
</tr>
<tr>
<td>Vd area** \text{V_d area**}</td>
<td>10.4</td>
</tr>
<tr>
<td>Transferrin mg Fe/24 h++</td>
<td>-</td>
</tr>
</tbody>
</table>

\*C_0: Calculated initial concentration
\text{tMRT:} Mean residence time
\text{V_d: Volume of distribution at steady state.}
\text{V_v: Volume of distribution of the central compartment.}
\text{V_d at: Volume of distribution during elimination.}
\text{Transferrin mg Fe/24 h++: Calculated amount of iron transported by transferrin.}
\text{umol/L: micromolar.}
\text{T_{1/2d}: terminal half life.}

The injected iron rapidly led to high serum iron levels with an average maximum value of 538 μmol iron/L at 10 minutes after the injection.

Serum transferrin did not change after the IV administration of iron as iron sucrose during the 24 hour study period, neither did the serum transferrin receptor concentration. The amount of iron transported by transferrin corresponded to 31.0% of the dose. Serum ferritin levels increased significantly after 8-10 hours and doubled after 24 hours.
Renal elimination of iron, which occurred only during the first 4 hours after injection, contributed very little to the overall elimination of iron (mean <5%). After 24 hours, urinary iron excretion was 5.19±1.28 mg, with the difference between that and the 24 hours prior to dosing being 4.68±1.31 mg. After 24 hours, 75 ± 11% of the dosage of sucrose was excreted, 91% of which was excreted within the first 4 hours after injection.

After 1 and 3 hours incubation of serum with 30, 60, and 150 µg iron in the form of iron sucrose, the total iron binding capacity (TIBC) of the serum decreased as the dose increased. At the 60 and 150 µg iron concentrations, TIBC decreased from 20 and 12 µmol iron/L at 1 hour, respectively, to <4 µmol iron/L at 3 hours for both.

These results show that, after a single intravenous dose of iron sucrose (Venofer®), iron is rapidly cleared from the serum and becomes available for biosynthesis of hemoglobin. Only a small fraction of the dose of iron is excreted in the urine.

6.5.2 Pharmacokinetics of ⁵⁹Fe-labeled Iron Sucrose


Krzysko et al. (1984) [4] reported the results of an open, cross-over pharmacokinetic study using iron sucrose (as Ferrum [Hausmann®] IV) 50 mg given to 11 healthy subjects, and 210 mg oral iron (Hemofer® prolongatum) as reference therapy. The results showed that intravenous iron was mainly distributed within the intracellular space. The serum concentration time curve could be well adapted to a two-compartment model. Table 11 summarizes the pharmacokinetics of radiolabeled iron sucrose (as Ferrum [Hausmann®]).

<table>
<thead>
<tr>
<th>Table 11 Selected Pharmacokinetic Parameters Following Intravenous Administration of 50 Mg Iron as Iron Sucrose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameters</strong></td>
</tr>
<tr>
<td>Initial Phase Constant (A)</td>
</tr>
<tr>
<td>Initial Phase Constant (B)</td>
</tr>
<tr>
<td>Fast Phase Constant (α)</td>
</tr>
<tr>
<td>Slow phase constant (β)</td>
</tr>
<tr>
<td>Blood→tissue distribution value (κ₁₂)</td>
</tr>
<tr>
<td>Tissue→blood distribution value (κ₂₁)</td>
</tr>
<tr>
<td>Low value of distribution volume of central compartment (Λ₁')</td>
</tr>
<tr>
<td>Total clearance of iron (Λ'K)</td>
</tr>
<tr>
<td>Overall distribution coefficient (Λ'area)</td>
</tr>
<tr>
<td>Half-life</td>
</tr>
<tr>
<td>Fraction of dose absorbed (F')</td>
</tr>
</tbody>
</table>

µg/mL: microgram per milliliters, kg: kilogram, h: hour.
6.5.3 Ferrokinetics Evaluated by Positron Emission Tomography


Beshara et al. (1997)[5] performed an open study of the pharmacokinetics and red cell utilization of $^{51}$Fe/$^{59}$Fe-labeled iron following a single intravenous administration of 100 mg iron as iron sucrose (Venofer®) in six patients (2 males and 4 females 24-63 years old) with iron deficiency and renal-failure-induced anemia. Using the Positron Emission Tomography (PET) technique, the iron kinetics were visualized and the iron distribution to organs of particular interest for iron and blood metabolism, such as the left ventricle of the heart, liver, bone marrow and spleen, was followed.

Emission scans of $^{52}$Fe, a partial positron emitter with a half-life of 8.3 h, were performed for the first 90 minutes, followed by scans at 3, 4, 5, 6, 7, and 8 hours. The distribution and kinetics of the labeled compound in the different organs could be followed and quantitative tissue iron uptake evaluated over time. The half-life of $^{59}$Fe of 45 days allowed a follow-up to determine red cell utilization of the injected labeled iron sucrose for 4 weeks (see Table 12). Samples were collected three times a week in the first week and twice a week in the following three weeks.

Table 12: The $^{59}$Fe Utilization Data

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4*</th>
<th>Patient 5</th>
<th>Patient 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>%</td>
<td>Day</td>
<td>%</td>
<td>Day</td>
<td>%</td>
</tr>
<tr>
<td>------</td>
<td>---</td>
<td>-----</td>
<td>---</td>
<td>-----</td>
<td>---</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>1</td>
<td>9</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>2</td>
<td>14</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td>3</td>
<td>29</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>64</td>
<td>6</td>
<td>66</td>
<td>6</td>
<td>43</td>
</tr>
<tr>
<td>9</td>
<td>62</td>
<td>9</td>
<td>88</td>
<td>9</td>
<td>56</td>
</tr>
<tr>
<td>13</td>
<td>69</td>
<td>13</td>
<td>90</td>
<td>13</td>
<td>62</td>
</tr>
<tr>
<td>16</td>
<td>91</td>
<td>16</td>
<td>87</td>
<td>15</td>
<td>59</td>
</tr>
<tr>
<td>20</td>
<td>82</td>
<td>21</td>
<td>86</td>
<td>21</td>
<td>66</td>
</tr>
<tr>
<td>23</td>
<td>97</td>
<td>24</td>
<td>94</td>
<td>24</td>
<td>68</td>
</tr>
<tr>
<td>28</td>
<td>89</td>
<td>28</td>
<td>64</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Erythrocyte concentrates given on day 10 to day 13 for severe anemia and excluded from the analysis after day 13, and was re-included on day 23.

The maximum radio-labeled iron red cell utilization ranged from 68-97% and was reached 15-28 days after iron sucrose administration. Two patients with iron deficiency anemia showed a utilization rate of 94% and 88%. The utilization rate in patients with
renal anemia or functional iron deficiency were 97% and 76%, or 68% and 76%, respectively.

Blood kinetics measured by PET in the left ventricle of the heart were found to be bi-exponential. In the liver, fast uptake occurred during the first 60 minutes, followed by a slower but steady increase. By the end of the PET analysis, the radioactivity uptake decreased slightly and reached 75% of the peak value. A comparable distribution of $^{52}\text{Fe}$/$^{59}\text{Fe}$-labeled iron sucrose with a fast uptake within 20 and 100 minutes was analyzed for the spleen and bone marrow.

A kinetic analysis using a three compartmental model (Patlak model), giving an estimate of the sizes of the reversible pools and the influx rate in the different tissues, showed a rather long distribution phase in the liver uptake, while immediate incorporation of the injected iron into the bone marrow could be detected.

An increase in serum ferritin and transferrin saturation levels above the baseline were seen in all patients after 24 hours and 1 week indicating a rapid competitive exchange of iron between $^{52}\text{Fe}$/$^{59}\text{Fe}$-labeled iron sucrose and the selective iron-binding proteins.

This study supports the finding that iron sucrose (Venofer®) has a suitable complex stability which allows a competitive exchange of iron between iron sucrose and selective iron-binding proteins such as transferrin and ferritin. The pharmacokinetic parameters show that the administered iron disappears very rapidly from the serum, thus ensuring a fast correction of iron deficiency anemia.

6.5.4 Efficacy, Tolerance, Serum Levels, Urinary Elimination of Iron.


Anatkov & Gekova (1970) [6] studied the efficacy, tolerance, serum levels, and urinary elimination of iron following intravenous administration of iron sucrose to 26 anemic patients, three males, 23 females, aged 16-60 years. The patients received a total of 1500-2000 mg of iron as iron sucrose in two dosage regimens: Five patients received 700-800 mg doses and 21 patients received 500 mg doses; iron was given over a period of three days infused over 3-4 hours. Laboratory investigations preceded infusion and then followed infusion at intervals that varied according to the specific measure being taken. These measures are summarized in Tables 13 and 14 and in Figures 5, 6, and 7.

Table 13 – Changes from Pre-Treatment for Hemoglobin

<table>
<thead>
<tr>
<th>Change from Baseline in Hb (g/dL)</th>
<th>Baseline Value</th>
<th>Average Change in Hemoglobin at 2, 4, and 6 Weeks After Administration of Iron Sucrose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6.2±1.13</td>
<td>2: +1.35*  4: +0.7*  6: +0.35*</td>
</tr>
</tbody>
</table>

Hb: hemoglobin, g: gram, dl: deciliter

* The values represent increases over baseline at week 2, increases over week 2 at week 4, and increases over week 4 at week 6. No standard deviation reported.
Table 13 shows that hemoglobin increased from pre-treatment levels as measured at various intervals after the study began. In addition, hematocrit increased over the first three weeks post-treatment to reach levels of over 40%; erythrocyte mass increased by 530 mL over six weeks post treatment; and the reticulocyte count rose from the first day after treatment to reach a maximum of 42-47% between the 9th and the 13th day, decreasing after the third week. Figure 5 illustrates the changes in hematocrit.

Figure 5  Hematocrit Before Treatment and at Weekly Intervals for Six Weeks After Treatment With Iron Sucrose

![Graph showing changes in hematocrit after treatment.]

Table 14  Mean Values for Serum Iron at Baseline and Weeks 5 and 8 Following IV Administration of Iron Sucrose

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline Value</th>
<th>Values At Weeks 5 and 8 After IV Iron Sucrose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Iron (µg/dL)</td>
<td>35 ± 18.1</td>
<td>98 ± 38.4, 98 ± 38.4</td>
</tr>
<tr>
<td>TIBC (µg)</td>
<td>522 ± 71.8</td>
<td>392 ± 38.4, 354 ± 17.8</td>
</tr>
</tbody>
</table>

TIBC: total iron binding capacity, µg: microgram, dL: deciliter.
# only value reported.

Iron parameters changed markedly during the study. Table 14 shows that serum iron rose and TIBC declined over the course of the study. On a short-term basis, serum iron varied considerably in the hours after infusion, as shown for the 500 mg dose in Table 15 and in Figure 6. There was a maximal serum iron concentration rise approximately 4 hours...
following a single intravenous dose of 500-800 mg iron sucrose which decreased to near baseline values within 48 hours.

Table 15. Short-Term Serum Iron Levels as a Function of Time After Iron Sucrose Infusion

<table>
<thead>
<tr>
<th>Time of Measure</th>
<th>Serum Iron Levels (μg/dL)</th>
<th>First Infusion</th>
<th>Second Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 Hours</td>
<td></td>
<td>1398 ± 605</td>
<td>1498 ± 692</td>
</tr>
<tr>
<td>24 Hours</td>
<td></td>
<td>440 ± 218</td>
<td>428 ± 228</td>
</tr>
<tr>
<td>48 Hours</td>
<td></td>
<td>103 ± 41</td>
<td>114 ± 51</td>
</tr>
<tr>
<td>72 Hours</td>
<td></td>
<td>77</td>
<td>94</td>
</tr>
</tbody>
</table>

Figure 6 - Serum Iron Level During and After the Infusion of 500 Mg of Iron Sucrose

The renal elimination of iron was found to be 4-6% of the administered dose, and the major fraction was excreted during the first day. Urinary elimination of iron varied according to the dose of iron as iron sucrose administered. At 24 hours after dosing, urinary iron rose from a baseline value of 201 μg iron for both dose groups to 22,427 μg iron for the 500 mg dose and to 33,687 μg iron for the 700 - 800 mg dose. The mean urinary elimination of iron was about 4.4% after initial doses, peaked at 6% after
subsequent doses. By the end of the second 24 hour period, urinary elimination of iron had declined to near pre-treatment levels. These results are illustrated in Figure 7.

Figure 7  Amount of Iron Eliminated in Urine

Adverse effects included headache, vomiting and muscular pain in three of 10 patients after they received 700-800 mg of study medication; transient circulatory collapse occurred in one patient. Mild headache and nausea in 7.8% of cases were observed following the 500 mg dose.

This study shows that IV iron sucrose can raise hematocrit, hemoglobin, reticulocyte count, erythrocyte mass, and serum iron, and lower total iron binding capacity, with relatively few side effects provided that individual doses of iron are maintained in the 500 mg range. The study also showed that the renal elimination of iron was 4.4 to 6% of the administered dose, most of which occurred during the first 24 hours after administration.
6.6 Other In Vivo Studies With Iron Sucrose

Five (includes two studies reporting results for the same patients) other in vivo studies with IV iron sucrose indicate that iron as iron sucrose is promptly available and continued administration provides the iron stores necessary for hemoglobin, serum iron, transferrin and ferritin levels in anemic patients. In addition, while no dose-ranging pharmacokinetic studies have been performed with iron sucrose, it has been shown that 300 mg iron as IV iron sucrose is well tolerated if infused over 2 hours, and doses as large as 400 and 500 mg iron may be safely administered if the infusion is performed over a longer period of time.

6.6.1 Table of Other In Vivo Studies
Table 16  Other In Vivo Studies: Dose-Tolerance Study

<table>
<thead>
<tr>
<th>Name of Company:</th>
<th>Name of Finished Product:</th>
<th>Name of Active substance(s):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luitpold Pharmaceuticals, Inc.</td>
<td>Venofer®</td>
<td>Iron Sucrose</td>
</tr>
</tbody>
</table>

### BIOPHARMACEUTICS STUDY SUMMARY

<table>
<thead>
<tr>
<th>OTHER IN VIVO STUDIES: DOSE-TOLERANCE STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref.</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>Alt. 7</td>
</tr>
</tbody>
</table>

N: number, mg: milligram, IV: intravenous.
Table 17  Other In Vivo Studies: Intravenous Iron Sucrose Versus Oral Iron and Erythropoietin

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Study -Investigator -Co-ordinating Center(s)</th>
<th>Design</th>
<th>Number of Subjects, Sex, and Age</th>
<th>Diagnosis and Criteria for Inclusion</th>
<th>Duration of Treatment</th>
<th>Test Product Dosage Regimen Route of Administration</th>
<th>Reference Therapy Dose Regimen Route of Administration</th>
<th>Criteria for Evaluation</th>
<th>Results</th>
<th>Safety</th>
</tr>
</thead>
</table>
| At. 8 | Internal report. 1993a. -Danielson, B. -Dept. of Medicine University Hospital, Uppsala, Sweden | Open comparative. | N=23  
Group 1=20  
Group 2=3  
13 males  
10 females  
50-79 years* mean 64 years* | Anemic patients with chronic renal failure on dialysis and on r-HuEPO treatment | Up to 105 weeks mean 81 weeks | Group 1: iron sucrose 100 mg iron IV over 2-5 minutes in 5-20 mL saline or in dialysis line 1-3 times weekly  
Test dose: 50 mg iron IV at end of dialysis | Group 2: ferrous sulphate 100 mg iron orally 1-3 times/daily | Hematological, biochemical, serum iron parameters, and safety variables | Group 1: Intravenous iron therapy gave prompt response in iron parameters and in erythropoiesis  
Group 2: Patients on r-HuEPO developed indications of functional iron depletion and were supplemented with oral iron to achieve an adequate hemoglobin response. | No adverse drug reactions observed. |

* These patients are a subset of the 110 patients included in Ref. 9, Danielson, 1993b.  
* Age range and mean for 29 patients in Group 1.  
N: number, mg: milligram, IV: Intravenous.
Table 18  Other In Vivo Studies: Efficacy and Tolerance Study in Dialysis Patients Receiving Erythropoietin

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Study -Investigator -Co-ordinating Center(s)</th>
<th>Design</th>
<th>Number of Subjects, Sex, and Age</th>
<th>Diagnosis and Criteria for Inclusion</th>
<th>Duration of Treatment</th>
<th>Test Product Dosage Regimen Route of Administration</th>
<th>Criteria for Evaluation</th>
<th>Results</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alt. 9</td>
<td>Internal report, 1993b. -Danielson BG -Department of Medicine University Hospital, Uppsala, Sweden</td>
<td>Open</td>
<td>N=110^a</td>
<td>Anemic patients with chronic renal failure treated with r-HuEPO</td>
<td>Up to 48 months Mean=12 months</td>
<td>Iron sucrose: test doses=50 mg iron 1IV2-5 minutes</td>
<td>Hematological parameters, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, serum iron, transferrin, ferritin, and all safety variables</td>
<td>Iron stores were effectively and promptly replenished.</td>
<td>Four patients experienced adverse effects: one transient metallic taste which stopped when infusion rate was extended to 3-5 minutes; one female with GI-symptoms, including vomiting and nausea and patient was discontinued from IV iron; one male with fever was withdrawn; one male with exanthema on the arms, legs and trunk without anaphylactoid reaction was withdrawn.</td>
</tr>
</tbody>
</table>

A: Pharmacokinetic results for 20 patients also presented. See Danielson 1993a for results.
N: number, mg: milligram, IV: Intravenous.
Table 19  Other In Vivo Studies: High and Low Dose Intravenous Iron Sucrose in Patients With and Without Iron Deficiency

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Diagnosis and Criteria for Inclusion</th>
<th>Duration of Treatment</th>
<th>Test Product Dosage Regimen Route of Administration</th>
<th>Reference Therapy Dose Regimen Route of Administration</th>
<th>Criteria for Evaluation</th>
<th>Results</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alt. 10</td>
<td>Al-Momen AK, Huralb SO, Mitiwalli AH, et al.</td>
<td>Open, dosage comparison</td>
<td>109</td>
<td>Hemodialysis patients on r-HuEPO for 8 weeks or longer</td>
<td>To a calculated dose for high dose; 2-3 weeks for low dose</td>
<td>Analyses performed at 4 weeks</td>
<td>Low dose: iron sucrose 100 mg iron IV over 1-4 hours once weekly up to the calculated dose</td>
<td>Changes in hematological parameters, serum iron, ferritin, and hematocrit</td>
<td>Significant rise in hemoglobin, hematocrit, serum ferritin in all patients. Iron deficient patients in both groups showed significant increase in mean corpuscular volume and mean corpuscular hemoglobin. In iron deficient patients, r-HuEPO could be reduced.</td>
<td>High dose group: after infusion two patients with feve, headache, nausea, hypotension, and urticaria; and during infusion three patients with headache, nausea, and skin discomfort. Low dose: No adverse reactions</td>
</tr>
</tbody>
</table>

N: number, mg: milligram, IV: intravenous.
### Table 20  Human Pharmacokinetic Studies: Long-Term Effects of Intravenous Iron Sucrose Complex Treatment

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Study - Investigator - Co-ordinating Center(s)</th>
<th>Design</th>
<th>Number of Subjects, Sex, and Age</th>
<th>Diagnosis and Criteria for Inclusion</th>
<th>Duration of Treatment</th>
<th>Test Product Dosage Regimen Route of Administration</th>
<th>Criteria for Evaluation</th>
<th>Results</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>All 11 Section 6</td>
<td>Amer. J. Kidney Diseases 1996; 27(2):234-238. Silverberg DS, Jain A, Peer G, et al. Department Nephrology Ichilov Hospital Tel Aviv, Israel</td>
<td>Open</td>
<td>N=34† 18 males 15 females Age 27-74 years</td>
<td>Anemic patients with moderate to severe chronic renal failure (creatinine clearance 10-40 mL/min) and hemoglobin &lt;11.0 g/dL</td>
<td>5 months</td>
<td>Iron sucrose, 200 mg iron IV in 150 mL saline over 2 hours once monthly for 5 months Total dose = 1000 mg iron Test dose: 25 mg iron IV in 100 mL saline over 1 hour</td>
<td>Serum creatinine, complete blood count, serum ferritin, serum iron, total iron-binding capacity, creatinine clearance every 3 and 6 months, and serum iron saturation</td>
<td>Significant improvement in anemia in 22/33 (66.7%) patients (responders): Hb rose from 9.9 g/dL to 11.1 g/dL at 6 months; hematocrit rose from 29.4% to 32.4% at 6 months; serum iron rose from 74.4 µg/dL to 84.2 µg/dL at 6 months. In 11 nonresponders, hematocrit and hemoglobin decreased.</td>
<td>One patient was excluded from the study due to mild reactions during infusion of the test dose. No other adverse reactions were reported. Four patients experienced hypertension requiring treatment with an antihypertensive agent.</td>
</tr>
</tbody>
</table>

†: One patient was excluded from the study following side effects after the test dose of iron sucrose.
N: number, mg: milligram, mL: milliliter, g: gram, min: minute, IV: intravenous.

**APPEARS THIS WAY ON ORIGINAL**
6.6.2 Dose-Tolerance Study in Dialysis Patients With Anemia


In an uncontrolled dose-tolerance study, Chandler et al (1998)[7] sought to determine how much iron as iron sucrose (Venofer®) could be administered intravenously within 2 hours without adverse events, with one objective being to establish the maximum tolerated dose of iron sucrose given within 2 hours.

The study was performed in 335 patients with anemia due to renal failure (including patients receiving hemodialysis, continuous ambulatory peritoneal dialysis, pre-dialysis, and transplant patients).

Patients received iron in doses of 200 mg (n=89), 300 mg (n=189), 400 mg (n=35), and 500 mg (n=22), all over 2 hours. The overall incidence of adverse reactions is presented in Table 21.

Table 21 Overall Incidence of Adverse Reactions Following Low and High Doses of IV Iron Sucrose

<table>
<thead>
<tr>
<th>Iron Sucrose Dose</th>
<th>Number of Patients</th>
<th>Number and Percent with Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg iron</td>
<td>89</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>300 mg iron</td>
<td>189</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>400 mg iron</td>
<td>35</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>500 mg iron</td>
<td>22</td>
<td>8 (36%)</td>
</tr>
</tbody>
</table>

Of those patients who experienced adverse reactions, the most common event was hypotension (9 patients). Other adverse events included nausea (5 patients), vomiting (3 patients), lower back pain (2 patients), back pain (1 patient), and bilateral edema of the hands and feet (1 patient). Two patients in the 500 mg group and one in the 400 mg group required hospitalization for 24 hours. All adverse effects are summarized in Table 22.
Table 22  Adverse Reactions to High Dose Iron Sucrose

<table>
<thead>
<tr>
<th>Patient (Age/Sex)</th>
<th>Iron Sucrose Dose (mg iron)</th>
<th>Reaction</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>27F</td>
<td>400 mg</td>
<td>Hypotension, abdominal and lower back pain, nausea and vomiting</td>
<td>Hospitalized 24 hours</td>
</tr>
<tr>
<td>43F</td>
<td>400 mg</td>
<td>Nausea and vomiting</td>
<td>Resolved in 30 minutes</td>
</tr>
<tr>
<td>76F</td>
<td>500 mg</td>
<td>Hypotension, nausea, vomiting</td>
<td>Hospitalized 24 hours</td>
</tr>
<tr>
<td>71M</td>
<td>500 mg</td>
<td>Hypotension</td>
<td>Resolved in 5 minutes</td>
</tr>
<tr>
<td>70M</td>
<td>500 mg</td>
<td>Hypotension, nausea</td>
<td>Resolved after 15 minutes</td>
</tr>
<tr>
<td>68F</td>
<td>500 mg</td>
<td>Hypotension, lower back pain</td>
<td>Resolved in 15 minutes</td>
</tr>
<tr>
<td>73F</td>
<td>500 mg</td>
<td>Hypotension</td>
<td>Resolved in 5 minutes</td>
</tr>
<tr>
<td>71F</td>
<td>500 mg</td>
<td>Hypotension</td>
<td>Resolved after 1 hour</td>
</tr>
<tr>
<td>34F</td>
<td>500 mg</td>
<td>Hypotension, nausea, back pain</td>
<td>Hospitalized 24 hours</td>
</tr>
<tr>
<td>32M</td>
<td>500 mg</td>
<td>Hypotension, bilateral edema of hands and feet</td>
<td>Resolved after 2 hours</td>
</tr>
</tbody>
</table>

M: males, F: females, mg: milligram.

The authors concluded that 200 mg or 300 mg doses of iron as iron sucrose infused over 2 hours were safe and well tolerated. However, doses of 400 mg and 500 mg iron, infused over 2 hours, were believed to have caused a transient iron overload which was responsible for the adverse reactions observed. The investigators suggested that larger doses might be safe if given over a longer period of time, i.e., to administer 400 mg iron over 2.5 hours and 500 mg over 3.5 hours.

6.6.3 Intravenous Iron Sucrose Study in Patients Intolerant to Oral Iron.


In an open comparative study, Danielson (1993a)[8, 9] studied 23 anemic patients with chronic renal failure who were receiving recombinant human erythropoietin and also showing an inadequate response or intolerance to oral iron. Twenty patients (11 men and 9 women, mean age 54 years, range 50-79 years) were switched from oral iron preparations to iron sucrose (as Ferrum [Hausmann®]) IV 100 mg iron administered intravenously once to three times weekly for variable durations (average 81 weeks). Three patients (2 men, 1 woman) continued on oral iron 100 mg one to three times a day.

Efficacy measures included the following:

- Hematological parameters: hemoglobin, red blood cell (RBC) count, hematocrit, leukocyte count, erythrocyte count, platelets, MCV, MCH, MCHC measured every one or two weeks.

- Chemistry parameters: serum iron, transferrin, ferritin, phosphate, among other chemical measures, measured every second or fourth week.
During treatment with oral ferrous sulfate, 20 patients showed iron depletion that did not respond to increased oral doses; some could not tolerate the increases. Subsequent IV iron sucrose treatment produced rapid increases in iron stores and improved or maintained hemoglobin levels and RBC volume. Data were presented as time courses of change in hemoglobin, ferritin, transferrin, and iron for each patient individually. Data from one patient showing the time course of these and related parameters as a function of the form of iron dosing are presented in Figures 8 and 9.

During treatment with EPO, three patients with initially high serum ferritin levels developed low serum iron, low transferrin saturation and a delayed response to erythropoietin. All three patients required supplemental oral iron treatment.

**Figure 8** For Patient No. 1, Time Course of Hemoglobin (Hb), Erythrocyte Particle (EPK), and Ferritin During Treatment With Ferrosulphate - Duroferon® (Oral Iron) and IV Iron-Sucrose (Ferrum [Hausmann®] IV, Ferrum).
Figure 9  For Patient No. 1, Time Course of Iron (Fe), Transferrin, and Ferritin During Treatment With Ferrosulphate Duroferon® (Oral Iron) and IV Iron Sucrose (Ferrum [Hausmann®] IV, Ferrum).

This study suggests that intravenous supplementation with iron sucrose produced a prompt improvement in hematological parameters in patients switched from oral iron therapy. The intravenous therapy was well tolerated. Iron sucrose provides an effective alternative to oral supplementation that can be used when oral iron therapy is ineffective or poorly tolerated.

6.6.4 Intravenous Iron Sucrose Study in Patients Receiving Erythropoietin


In an open dosage comparison study of the safety and efficacy of iron sucrose (Ferosac® which manufactured by SPIMACO, Riyadh, Saudi Arabia, and is identical to Venofer®), Al-Momen et al (1994) [10] enrolled 109 hemodialysis patients receiving erythropoietin (57 males, 52 females, mean age 34.1 ± 11.7 years). Sixty four of these patients were iron-deficient.

Group 1 (n=58; "high dose") received 500 mg of iron as iron sucrose in 250 ml normal saline intravenously over 1-4 hours once weekly until a target total dose based upon
hemoglobin levels was reached. Group 1 was subdivided into an iron deficient group receiving a high erythropoietin dose (up to 100 IU/kg 3 times weekly for at least 8 weeks; n=42), and a non-iron deficient group receiving a low erythropoietin dose (50 IU/kg 3 times per week for at least 8 weeks; n=16).

Group 2 (n=51; "low dose") received 100 mg iron as iron sucrose in 25 ml normal saline intravenously over 5-10 minutes three times weekly for a maximum of 5 to 10 doses. Group 2 was also subdivided into an iron deficient group receiving high erythropoietin doses (n=22), and a non-iron deficient group receiving low erythropoietin doses (n=29).

Variables measured included serum iron, total iron binding capacity, serum ferritin, hemoglobin, and hematocrit. Results are presented in Table 23.

Table 23  Comparison Between Hematological and Iron Parameters Before and Four Weeks After Beginning Iron Sucrose Therapy

<table>
<thead>
<tr>
<th>Test</th>
<th>Group 1 - &quot;High Dose&quot; - 500 Mg Iron (N=58)</th>
<th>Group 2 - &quot;Low Dose&quot; - 100 Mg Iron (N=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Iron Deficient (n=42)</td>
<td>Non-Iron Deficient (n=16)</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>A ± B</td>
<td>A ± B</td>
</tr>
<tr>
<td>8.3±0.7</td>
<td>11.0±0.7</td>
<td>8.8±0.6</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>24.9±2.3</td>
<td>33.0±2.1</td>
</tr>
<tr>
<td>MCV (fL)</td>
<td>71.7±4.7</td>
<td>81.4±3.5</td>
</tr>
<tr>
<td>MCH (pg)</td>
<td>24.5±2.7</td>
<td>30.9±1.5</td>
</tr>
<tr>
<td>Fe(µmol/L)</td>
<td>11.0±2.9</td>
<td>18.7±4.6</td>
</tr>
<tr>
<td>TIBC (µmol/L)</td>
<td>80.4±5.3</td>
<td>57.9±9.8</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>18.6±11.8</td>
<td>52.2±25.3</td>
</tr>
</tbody>
</table>

* A = before iron sucrose therapy; B = Four weeks after beginning iron sucrose therapy.
* *p<0.001 (Student's paired "t" test for B vs A).
Hb: hemoglobin; Hct: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; Fe: iron; TIBC: total iron binding capacity
µg/dL: gram per deciliter, µmol/L: micromolar, ng/mL: nanogram per milliliter, mg: milligram.

The results showed a significant rise in all parameters measured in both the high dose and low dose patients of the iron deficient group (Group 1) after 4 weeks of therapy. For both high and low dose patients in the non iron deficient group (Group 2), there was a significant rise in hemoglobin and hematocrit.

Two patients in Group 1 developed fever, headache, nausea, hypotension, and urticaria that responded to antihistamines and hydrocortisone and the reaction disappeared within a few hours. Three other patients in the high dose group developed headache, nausea, and skin discomfort after two hours during the infusion. The symptoms disappeared when the infusion was stopped. The low dose (100 mg iron)-Group 2 patients experienced no adverse reactions.

This study suggests that intravenous iron supplementation with iron sucrose complex increases hematocrit in hemodialysis patients who had shown a poor response to erythropoietin. The results suggest that iron sucrose complex is a safe and effective intravenous iron formulation for these patients, even if they are not iron deficient.
6.6.5 Effects of Intravenous Iron Sucrose on Anemia of Chronic Renal Failure


In an open study, Silverberg et al (1996)[11] measured hematopoietic and other parameters in 33 anemic patients (18 male, 15 female, age range 27-74 years) receiving infusions of iron as iron sucrose (Ferrum [Hausmann®] IV) without concomitant administration of erythropoietin. Patients were included in the study if hemoglobin levels were <11.0 g/dL and creatinine clearance ranged between 10 to 40 mL/min (moderate to severe chronic renal failure). All patients had been receiving a slow-release oral iron preparation consisting of 160 mg ferrous sulfate two times daily (100 mg iron per day). For the study, patients received 200 mg of iron intravenously in 150 mL saline over 2 hours once monthly for five months for a total of 1000 mg per patient. Prior to entering the study, patients received a test dose of 25 mg iron as iron sucrose in 100 mL saline over 60 minutes.

Laboratory measures and calculations included blood pressure, serum creatinine, creatinine clearance, hematocrit, hemoglobin, complete blood count, serum ferritin, iron, total iron binding capacity, and percentage of iron saturation from six months before until six months after beginning treatment, at three month intervals. Results are shown in Table 24.

Table 24 Serum Iron and Hematological Parameters in Chronic Renal Failure Patients Receiving Intravenous Iron Sucrose

<table>
<thead>
<tr>
<th>Parameter‡</th>
<th>Time of Measure</th>
<th>Initial‡</th>
<th>+3 Months</th>
<th>+6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>29.6±2.8</td>
<td>31.4±2.6</td>
<td>31.5±3.1 *</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.6±1.1</td>
<td>10.5±0.9</td>
<td>10.6±1.1 *</td>
<td></td>
</tr>
<tr>
<td>Serum Iron (ug/dL)</td>
<td>76.1±5.1</td>
<td>78.1±4.9</td>
<td>85.1±5.1 *</td>
<td></td>
</tr>
<tr>
<td>TIBC (ug/dL)</td>
<td>343.7±60.0</td>
<td>306.4±18.1</td>
<td>311.6±40.7 *</td>
<td></td>
</tr>
<tr>
<td>Iron Saturation (%)</td>
<td>22.1±7.1</td>
<td>25.5±8.1</td>
<td>27.3±8.2 *</td>
<td></td>
</tr>
<tr>
<td>Serum Ferritin (ug/L)</td>
<td>106±95</td>
<td>190.4±108.0 *</td>
<td>297±192 *</td>
<td></td>
</tr>
</tbody>
</table>

* Data are presented as means ± standard deviations.
‡ Values determined immediately before onset of treatment.
* P<0.01 by two-tailed Student's paired t-test, at least compared to initial values.

Following three months of treatment, TIBC, iron saturation, and serum ferritin had improved to a statistically significant degree. By six months, these measures and hematocrit, hemoglobin, and serum iron had improved to a statistically significant degree. Serum creatinine and creatinine clearance did not change throughout the study. Statistical calculations were carried out on data from all 33 patients together and the significant findings emerged even though 11 of these patients, "nonresponders", had no statistically significant change in any laboratory measure when considered apart from the
remaining 22 patients, the "responders". Table 24 summaries are for all patients; responders as well as non-responders, taken together.

No adverse events were reported among the 33 patients enrolled and treated in this study; however, a 34th patient experienced nausea and sweating during infusion of the test dose and was not enrolled in the study; no further data were recorded for this patient. Four patients developed an increase in blood pressure requiring antihypertensive drug therapy adjustment.

This study suggests that iron sucrose is a safe and effective agent for treating anemia for patients with moderate to severe chronic renal failure who are not receiving dialysis. Hematocrit and hemoglobin rose significantly by 3 months and serum iron, TIBC, iron saturation, and serum ferritin by 6 months after starting 200 mg iron once monthly for 5 months.

6.7 In Vitro Studies

6.7.1 In Vitro Binding of Iron Sucrose to Human Transferrin
Van Iperen CE, van Dijk AJG, and Marx JIM. In vitro binding of iron saccharate to human transferrin. Communication
Geisser P. Comments on the publication from C.E. van Iperen et al. "In vitro binding of iron saccharate to human transferrin". Personal communication.

This study [12] examined the in vitro binding of iron sucrose to human transferrin at 37°C for up to 30 hours. After 1-6 hours, a substantial portion of apotransferrin was still unsaturated and only after 30 hours were one or both of the transferrin binding sites occupied. The authors considered that iron does not readily bind to transferrin in vitro, but rather may need to be taken up by macrophages or hepatocytes to become available to bind to transferrin, the molecular form of iron needed for uptake by erythroid cells.

In a response to this publication, Dr. Geisser [13] indicated that the above results are inconsistent with (1) the evidence of complete saturation of transferrin by iron following incubation of iron sucrose in serum at 37°C and (2) the detection of iron by PET scan in the bone marrow of minipigs within 5-10 minutes of administration. These differences serve to point out that in vitro and in vivo results cannot necessarily be compared.

6.8 Drug Formulation

Iron sucrose [marketed as Venofer®, and Ferrum [Hausmann®] IV, Veno-Ferrum®, and Hippiron® (veterinary product)] is a brown, aqueous solution containing iron (III)-hydroxide sucrose complex as the active ingredient and water for injection. The sterile solution has an osmolality of 1250 mosm/L and a pH of 10.5-11.1. No preservatives are added and for pH adjustment a solution of is used. If prepared as an infusion, Venofer® must solely be diluted in 0.9% sodium chloride solution. Venofer® is supplied
in 5 ml vials containing a sterile solution of iron as iron sucrose (100 mg iron corresponding to 2% weight/volume). Vials should be stored in the original carton at 25°C or below and should not be frozen.

Venofer®, iron sucrose (iron(III)-hydroxide sucrose complex), consists of an aqueous colloidal dispersion of polynuclear ferric hydroxide cores surrounded by non-covalently bound sucrose molecules [(Fe₃O₄H·4(H₂O))] in a saturated sucrose solution at pH 10.5 – 11.1. The exact structural formula is not known. Iron sucrose has a molecular weight of 43,000 daltons and based on its chemical composition and stoichiometry of the chemical reaction used in its manufacture, its molecular formula is [NaₚFe₃O₈(OH)ₓ·x(H₂O)]ₖ·m(C₁₂H₂₅O₁₁) where: p = 2.30; r = 7; x = 2.70; L = 8.60; m = 112.23.

The formulations of Venofer® utilized in the preclinical and clinical studies sponsored by Vifor (International), Inc. are detailed in Attachment C.
### Attachment C DRUG FORMULATION DEVELOPMENT SUMMARY

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Lot. No.</th>
<th>Dosage Form and Strength</th>
<th>Batch Size/Manufacturer &amp; Site</th>
<th>Formulation or Significant Manufacturing Change (if any) and Reason for Change</th>
<th>Effect of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berrière J. et al (Report. 12.3.1998)</td>
<td>335109 A1</td>
<td>Venofer® IV</td>
<td>100 mg iron/5 ml. ampule</td>
<td></td>
<td>Not applicable</td>
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<tr>
<td>Itzhara S. et al (Internal Report. 14.5.1997)</td>
<td>671109</td>
<td>Venofer® IV</td>
<td>100 mg iron/5 mL ampule</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Chandler G. et al (Internal Report. VII95002, 1998)</td>
<td>572109 670109 675109</td>
<td>Venofer® IV</td>
<td>100 mg iron/5 mL ampule</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Danielson B.O. et al (Internal Report. 7.7.1995)</td>
<td>443209-B1</td>
<td>Venofer-rum</td>
<td>100 mg iron/5 mL ampule</td>
<td></td>
<td>Not applicable</td>
</tr>
<tr>
<td>Hussain et al, 1999</td>
<td>558109 A2</td>
<td>Venofer-rum</td>
<td>100 mg iron/5 mL ampule</td>
<td></td>
<td>Not applicable</td>
</tr>
<tr>
<td>Macdougall I.C. et al (Internal Report. March 5, 1999)</td>
<td>333109 A1 692109 A1 554209 A2</td>
<td>Venofer® IV</td>
<td>100 mg iron/5 mL ampule</td>
<td></td>
<td>Not applicable</td>
</tr>
<tr>
<td>Meyer M.F. et al (publication) 1996</td>
<td>443209 A1</td>
<td>Venofer-rum</td>
<td>100 mg iron/5 mL ampule</td>
<td></td>
<td>Not applicable</td>
</tr>
<tr>
<td>DePree et al, 1997</td>
<td>293209</td>
<td>Ferrum IV</td>
<td>100 mg iron/5 mL ampule</td>
<td></td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

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a: Ferrum IV, Venofer-rum and Venofer IV are identical products.
<table>
<thead>
<tr>
<th>Study Number</th>
<th>Lot No.</th>
<th>Dosage Form and Strength</th>
<th>Batch Size/Manufacturer &amp; Site</th>
<th>Formulation or Significant Manufacturing Change (if any) and Reason for Change</th>
<th>Effect of Change</th>
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<tr>
<td>Ait-Momen et al, 1999</td>
<td>Not known</td>
<td>Not known</td>
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<td>Not applicable</td>
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<tr>
<td>Schaefer R.M. et al, (Study Report, 1999)</td>
<td>670109</td>
<td>Venofer IV 100 mg iron/5 mL ampule</td>
<td></td>
<td></td>
<td>None</td>
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<tr>
<td>Van Zyl-Stnit V R et al, (Study Report, VENO/BOSSA-V/1/001 FARMOVIS 52/93, May 26, 1997)</td>
<td>447209 A1</td>
<td>VenoFerrum 100 mg iron in 5 mL ampule</td>
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<td>None</td>
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<tr>
<td>LU98001</td>
<td>RD98003</td>
<td>Venofer IV 100 mg iron/5 mL vial</td>
<td>Filling of vials under rubber stoppers used.</td>
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<tr>
<td></td>
<td>RD98012</td>
<td>VenoFerrum IV 100 mg iron/5 mL vial</td>
<td></td>
<td></td>
<td>None</td>
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<td>LU98002</td>
<td>RD98012</td>
<td>Venofer IV 100 mg iron/5 mL vial</td>
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<td>Preclinical Studies</td>
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<td>Not applicable</td>
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<td>Arzenein-Forsch/Drug 1992</td>
<td>950208</td>
<td>Ferrum IV 100 mg iron in 5 mL ampule</td>
<td></td>
<td></td>
<td>Not applicable</td>
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<tr>
<td>VFR 17/736 January 15, 1995</td>
<td>330109 A2</td>
<td>Ferrum IV 100 mg iron in 5 mL ampule</td>
<td></td>
<td></td>
<td>Not applicable</td>
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<tr>
<td>VFR 2/951739 January 15, 1995</td>
<td>330109 A2</td>
<td>Ferrum IV 100 mg iron in 5 mL ampule</td>
<td></td>
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<td>Not applicable</td>
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<tr>
<td>VFR 4/950317 June 7, 1995</td>
<td>330109 A2</td>
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<td>Not applicable</td>
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<tr>
<td>VFR 3A9513491 December 20, 1995</td>
<td>330109 A2</td>
<td>Ferrum IV 100 mg iron in 5 mL ampule</td>
<td></td>
<td></td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

a: Ferrum IV, VenoFerrum and Venofer IV are identical products.
### Attachment C DRUG FORMULATION DEVELOPMENT SUMMARY (continued)

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Lot No.</th>
<th>Dosage Form and Strength</th>
<th>Batch Size/Manufacturer &amp; Site</th>
<th>Formulation or Significant Manufacturing Change (if any) and Reason for Change</th>
<th>Effect of Change</th>
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<tbody>
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<td>VFR 5951735</td>
<td>330109 A2</td>
<td>Ferrum IV 100 mg iron in 5 mL ampule</td>
<td></td>
<td>Not applicable</td>
<td>None</td>
</tr>
<tr>
<td>December 21, 1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>VFR 012/1211</td>
<td>572109</td>
<td>Venofer® IV 100 mg iron in 5 mL ampule</td>
<td></td>
<td>Due to change in manufacturing site from where ampules were no longer manufactured, to</td>
<td>None</td>
</tr>
<tr>
<td>January 10, 1997</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>VFR 014/91264</td>
<td>572109</td>
<td>Venofer® IV 100 mg iron in 5 mL ampule</td>
<td></td>
<td>Due to change in manufacturing site from where ampules were no longer manufactured, to</td>
<td>None</td>
</tr>
<tr>
<td>April 29, 1997</td>
<td></td>
<td></td>
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<td>VFR 15972408</td>
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<td>Due to change in manufacturing site from where ampules were no longer manufactured, to</td>
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<tr>
<td>September 18, 1997</td>
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<tr>
<td>VFR 16974254</td>
<td>676109</td>
<td>Venofer® IV 100 mg iron in 5 mL ampule</td>
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<td>Due to change in manufacturing site from where ampules were no longer manufactured, to</td>
<td>None</td>
</tr>
<tr>
<td>December 29, 1997</td>
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<td>SR-1020/L591</td>
<td>572109</td>
<td>Venofer® IV 100 mg iron in 5 mL ampule</td>
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<td>Due to change in manufacturing site from where ampules were no longer manufactured, to</td>
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</tr>
<tr>
<td>December 9, 1997</td>
<td></td>
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</tbody>
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a: Ferrum IV, VenoFerrum and Venofer IV are identical products.

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**APPEARS THIS WAY ON ORIGINAL**
6.9 Analytical Methods

The analytical methods used in Vifor (International), Inc.-sponsored studies for the
determination of serum iron, urine sucrose and $^{52}$Fe radiolabeled iron sucrose are detailed
in Attachment D.

6.10 Dissolution

Dissolution data are not applicable as iron sucrose is an aqueous colloidal dispersion of
polynuclear ferric hydroxide cores surrounded by non-covalently bound sucrose
molecules in a saturated sucrose solution at pH 10.5 – 11.1.
## Attachment D IN VIVO ANALYTICAL METHODS SUMMARY

<table>
<thead>
<tr>
<th>Name</th>
<th>Submission Date</th>
<th>Type of Biol. Fluid</th>
<th>Method</th>
<th>Sensitivity of Method/Range</th>
<th>Specificity (parent/metabolites)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macdougall et al, March 5, 1999</td>
<td></td>
<td>Serum</td>
<td></td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>1. Iron</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Total circulating iron</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Hemoglobin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Serum ferritin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Danielson et al, 1995</td>
<td>October 15, 1998</td>
<td>1. Serum and urine</td>
<td></td>
<td>1. Sensitivity: 10-1000μmol/L; relative standard deviation of method: 5.64% (n=63),</td>
<td>Iron (no metabolites)</td>
</tr>
<tr>
<td>1. Elemental iron</td>
<td></td>
<td>2. Urine</td>
<td></td>
<td>x̅=25.8μmol/L, SD: 44μmol/L</td>
<td></td>
</tr>
<tr>
<td>2. Sucrose</td>
<td></td>
<td>3. Serum</td>
<td></td>
<td>2. Not reported</td>
<td></td>
</tr>
<tr>
<td>3. Transferrin receptor</td>
<td></td>
<td>4. Serum</td>
<td></td>
<td>3. Normal range: 1.54 ± 0.43 mg/L (95% confidence intervals: 0.85-3.05 mg/L)</td>
<td></td>
</tr>
<tr>
<td>4. Total iron binding capacity</td>
<td></td>
<td></td>
<td></td>
<td>4. Not reported</td>
<td></td>
</tr>
<tr>
<td>Beshara et al, 1997</td>
<td>October 15, 1998</td>
<td>1. Whole blood,</td>
<td></td>
<td>1. Not reported</td>
<td></td>
</tr>
<tr>
<td>1. ^55^Fe/^55^Fe</td>
<td></td>
<td>plasma, packed red</td>
<td></td>
<td>2. Not reported</td>
<td></td>
</tr>
<tr>
<td>2. Iron status: Serum iron,</td>
<td></td>
<td>cells, liver, left</td>
<td></td>
<td>3. Normal range: 1.54 ± 0.43 mg/L (95% confidence intervals: 0.85-3.05 mg/L)</td>
<td></td>
</tr>
<tr>
<td>total iron binding capacity,</td>
<td></td>
<td>ventricle of heart</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>transferrin saturation, serum</td>
<td></td>
<td>bone marrow, spleen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Serum transferrin receptor</td>
<td></td>
<td>2. Serum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Serum ferritin</td>
<td></td>
<td>3. Serum</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

WHO=World Health Organization; Fe=iron; Mn=manganese; Ga=gallium; Ge=germanium
### Attachment D In Vivo Analytical Methods Summary (continued)

<table>
<thead>
<tr>
<th>Parent Drug: Iron sucrose Study/Test</th>
<th>Submission Date</th>
<th>Type of Biological Fluid</th>
<th>Method</th>
<th>Sensitivity of Method/Range</th>
<th>Specificity (parent/metabolites)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major et al, 1997</td>
<td>October 15, 1998</td>
<td>Blood red cells, reticulocytes; serum</td>
<td>Not reported</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Chandler C, Harcowski J and MacDougall K, VIF95002, 1998</td>
<td>October 15, 1998</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td></td>
</tr>
<tr>
<td>1. Hematological Indices 2. Serum chemistry tests 3. Intact PTH 4. Aluminum</td>
<td></td>
<td></td>
<td>2. Reference values for serum phosphate and serum alkaline phosphatase: 0.76-1.64 mmol/L and 0.8-4.8 μkat/L; serum calcium adjusted for albumin with 0.019 mmol/L for each g/L deviation of serum albumin from the normal mean of 46 g/L (reference value for serum calcium: 2.20-2.60 mmol/L). 3. Reference range: 10-55 ng/L 4. Normal value &lt;10 μg/L.</td>
<td>3. Reference range: 10-55 ng/L 4. Normal value &lt;10 μg/L.</td>
<td></td>
</tr>
</tbody>
</table>
## Attachment D: In Vivo Analytical Methods Summary (continued)

**Manufacturer:** Luipold Pharmaceuticals, Inc. Venofer®

<table>
<thead>
<tr>
<th>Study/Test</th>
<th>Submission Date</th>
<th>Type of Biological Fluid</th>
<th>Method</th>
<th>Sensitivity of Method/Range</th>
<th>Specificity (parent/metabolites)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hematological parameters</td>
<td></td>
<td>Serum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Serum iron, Iron binding capacity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Ferritin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silverberg et al, 1996.</td>
<td>October 15, 1998</td>
<td>Blood, Serum</td>
<td>Not reported</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Complete blood count, creatinine, ferritin, total iron binding capacity, creatinine clearance, iron saturation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
This section provides the approved package insert for Venofer® for the countries listed below:

Within the European Continent:
1. Bulgaria
2. Cyprus
3. France
4. Germany
5. Hungary
6. Netherlands
7. Portugal
8. Romania
9. Russia
10. Slovakia
11. Slovenia
12. Switzerland
13. United Kingdom

Outside the European Continent:
1. Australia
2. Bolivia
3. Chile
4. Columbia
5. Dominican Republic
6. Ecuador
7. El Salvador
8. Guatemala
9. Hong Kong
10. India
11. Iraq
12. Israel
13. Lebanon
14. Panama
15. Peru
16. Saudi Arabia
17. South Korea
18. Sri Lanka
19. Thailand
20. Tunisia
21. Turkey
22. Uruguay
VENOFER® PACKAGE INSERT FOR:

AUSTRALIA
**Venofer**

**intravenous**

**Composition**
Standardized aqueous alkaline solution of Ferric-Hydroxide-Sucrose Complex. One ampoule of 5 ml contains 100 mg trivalent iron.

**Action**
The polynuclear ferric-hydroxide is partly stored as ferritin (depot iron) after com-
plex formation with the protein ligand apfer-
ritin of the mitochondria of the liver.
Iron is transported in the blood plasma bound to β-globulin, transferrin. This pro-
tein reacts with two atoms of iron per pro-
tein molecule, with the formation of a pink-
 coloured complex. The major function of transferin is to act as the carrier of iron through the body transportation to the sites of haemoglobin- and myoglobin-syn-
thesis as well as to the cells, producing iron containing enzymes. In doing this, it plays a vital and central role in iron metabolism.
Transferrin also has a second important function, that of participating in the body's defence mechanism against infection.
The haemoglobin synthesis increases quicker and with more certainty than after peroral therapy with ferrous salts, although the kinetics of the iron incorporation is independent on the way of iron adminis-
tration.

**Indication**
All cases of iron deficiency in which rapid and reliable substitution of iron is required, more particularly for the following:
- severe iron deficiency, e.g. after haemor-
   rhage;
- disturbances in iron absorption in the gastro-intestinal tract;
- marked incompatibility of oral iron prepa-
   rations;
- iron deficiency resistant to treatment, when the patient cannot be relied on to take the tablets, and
- contacts between doctor and patient at irregular intervals.

**Dosage**
1st day: 2.5 ml = 50 mg Fe(III)
2nd day: 5.0 ml = 100 mg Fe(III)
3rd day: 10.0 ml = 200 mg Fe(III)
to be followed with 10 ml two times a week depending on hemoglobin level.

**Posology**
On a 4th, administration of 100 mg Fe(III) (= 1 ampoule of 5 ml) results in an in-
crease of the haemoglobin level of 2-3%,
during pregnancy of 2% respectively.
In order to avoid overdosage the maximum
dose may be determined with the following
method or according to the following table.
The dosage required may be calculated on the basis of a normal haemoglobin value of 15 g/100 ml at a blood volume estimated at 7% of the body weight, a haemoglobin iron content of 0.34% and the need for an iron depot of 500 mg.

**Total dosage in mg Fe**
(see also table)
The blood dosage of iron has been calculat-
ed from the following formula:

![Formula](https://via.placeholder.com/150)

**Mode of action**
L'hydroxy feerrique polynuclear est en partie emmagasine sous forme de ferritine (fer de réserve) après formation d'un com-
plexe avec le colloide protéïnique des mito-
chondries du foie, l'apoferritine.
Dans le plasma sanguin, le fer est trans-
porté lié à la β-globuline: la transferrine.
Cette protéine est capable de fixer deux atomes de fer par molécule, avec forma-
tion d'un complexe de couleur rose.
La transferrine (pour fonction essentielle de véhiculer le fer dans l'organisme transport vers les lieux de synthèse de l'hémoglobi-
ne et de la myoglobine et vers les cellules productrices d'enzymes contenant du fer).
De ce fait, elle joue un rôle capital pour le métabolisme du fer. Sa deuxième fonction importante est représentée par sa partici-
pation aux mécanismes de défense du corps contre les infections.
Après emploi du Venofer I.V., le taux d'hé-
moglobine s'élève plus rapidement et plus sûrement qu'après traitement aux seuls fer-
reux par voie orale, bien que les processus cinétiques de résorption du fer soient indé-
péndants de son mode d'administration.

**Indication**
Tous les cas de carence matérielle où une administration de fer rapide et sûre s'avère nécessaire:
- spécialement lors d'états de carence grave, a fortiori par exemple,
- lors de troubles d'absorption dans le tractus gastrointestinal,
- lors de troubles de recherche nette à l'administra-
tion orale de fer,
- lors d'un état de carence matérielle resis-
tant au traitement par os, au cours duquel l'absorbance du malade peut être mise en jeu,
- lors de l'examen des laboratoires médicaux sont trop espacés et irréguliers.

**Rythme d'administration**
1er jour: 2.5 ml = 50 mg de Fe(III)
2ème jour: 5.0 ml = 100 mg de Fe(III)
3ème jour: 10.0 ml = 200 mg de Fe(III)
Poursuivre l'administration à raison de 10 ml deux fois par semaine pour une durée totale fixée en fonction du taux d'hémoglo-
bine.

**Posología**
En moyenne, l'administration de 100 mg de Fe(III) (soit une ampoule de 5 ml) permet une élévation du taux d’hémoglobine de 2 à
3%, et de 2% en période de grossesse.
Afin d’éviter un surdosage, la dose maxi-
male à utiliser peut être calculée selon la méthode ci-après ou à l’aide du tableau ci-
dessous.
La dose utile peut-être déterminée sur la base des estimations suivantes: taux nor-
mal d'hémoglobine: 15 g/100 ml pour un volume de sang correspondant à 7% du poids total du corps; taux de fer dans l'hé-
moglobine: 0.34%; nécessité d'une quan-
tité de fer de réserve égale à 500 mg.

**Dosis totales de fer en mg**
(vea también tabla inferior)
El calcule a été effectué en utilisant la for-
mule suivante:

![Formula](https://via.placeholder.com/150)

**Indicaciones**
En todos los casos de deficiencia de hierro, en los cuales una sustitución rápida y segu-
ra es necesaria:
- En particular, en casos graves de defi-
   ciencia de hierro, como p.ej. después de pérdidas de sangre,
- En casos de dificultad de resorción gastrointestinal referente al hierro,
- En casos de intolerancia a la administra-
tión oral de preparados de hierro,
- En casos de deficiencia de hierro refrac-
torias al tratamiento, en los cuales el médic
   no puede farse en la disciplina del enferme-

**Posología**
Normalmente, la administración de 100
mgs. de Fe(III), correspondiente a una
ampolla de 5 cc., consigue aumentar en
2-3% el nivel de hemoglobina y un 2% en
el caso de embarazadas.
Con el fin de evitar una dosificación
demasiado fuerte, se puede calcular la
dosis máxima utilizando el método o el
cuadro de más abajo.
La dosis necesaria puede determinarse a
base de un nivel de hemoglobina normal
de 15 g/100 cc. para un volumen de san-
gre, estimado en un 7% del peso del cuerpo,
un porcentaje de hierro en la hemoglobina
de 0,34% y la necesidad de una cantidad de
hierro retardo de 500 mg.

**Dosis total en mg de fer**
(vea tambien tabla inferior)
La dosis total de hierro ha sido calculada
en base a la siguiente fórmula:

![Formula](https://via.placeholder.com/150)
**Total iron deficiency in mg**

Hb-iron deficiency (in mg) = body weight (kg) x (normal Hb – actual Hb in g/l) x 0.24

This calculation is based on:
- a normal Hb 150 g/l for body weights higher than 35 kg resp. 130 g/l up to 34 kg body weight
- the iron content of haemoglobin (0.34%)
- the blood volume (approx. 7% of the body weight)
- and the requirements of depot iron (approx. 15 mg per kg up to a weight of about 34 kg, total of 500 mg above 34 kg).

- Factor 0.24 = 0.0034 x 0.07 x 1000

Example

Patient weighing 70 kg
normal Hb: 150 g/l
actual Hb: 80 g/l
Hb deficit: 70 x (150-50) x 0.24 = 1176 mg Fe
Need for depot iron: 500 mg Fe
Total dosage: 1676 mg Fe

Therefore this patient requires 1700 mg iron or 17 ampoules during treatment.

**Daily maximum doses**

Children up to 5 kg 1.25 ml (1/4 ampoule)
Children between 5-10 kg 2.5 ml (1/2 ampoule)
Adults 10.0 ml (2 ampoules)

**Side effects**

In rare cases anaphylactoid reactions have been observed. The counter-measurements to be taken are the same as with any anaphylaxis.

**Precautions**

In cases of inappropriate storage, formation of sediments cannot be excluded. There are examine ampoules before injecting (especially top and bottom part of the ampoules). Expired ampoules or those containing sediments must not be injected under any circumstances. Recommended storage temperature between 4 – 25°C.

Do not mix Venoferr® with any other medicament.

**Centre-indications**

All cases of iron overload or disturbances in utilization of iron.

**Commercially available**

5, 50 and 100 ampoules, each 5 ml/100 mg of iron.


<table>
<thead>
<tr>
<th>Body weights/Poids du corps/Peso corporal</th>
<th>5 kg</th>
<th>10 kg</th>
<th>15 kg</th>
<th>20 kg</th>
<th>25 kg</th>
<th>30 kg</th>
<th>35 kg</th>
<th>40 kg</th>
<th>45 kg</th>
<th>50 kg</th>
<th>55 kg</th>
<th>60 kg</th>
<th>65 kg</th>
<th>70 kg</th>
<th>75 kg</th>
<th>80 kg</th>
<th>85 kg</th>
<th>90 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb = 60 g/l</td>
<td>Amp.</td>
<td>1.5</td>
<td>3</td>
<td>5</td>
<td>6.5</td>
<td>8</td>
<td>9.5</td>
<td>12.5</td>
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<td>17</td>
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<td>19</td>
<td>20</td>
<td>21</td>
<td>22.5</td>
<td>23.5</td>
</tr>
<tr>
<td>Hb = 75 g/l</td>
<td>Amp.</td>
<td>1.5</td>
<td>3</td>
<td>4.5</td>
<td>5.5</td>
<td>7</td>
<td>9.5</td>
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<td>15</td>
<td>16</td>
<td>17</td>
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<td>19</td>
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<td>21</td>
<td>22.5</td>
<td>23.5</td>
</tr>
<tr>
<td>Hb = 90 g/l</td>
<td>Amp.</td>
<td>1.5</td>
<td>2.5</td>
<td>4.5</td>
<td>6</td>
<td>7.5</td>
<td>10</td>
<td>11</td>
<td>11.5</td>
<td>13</td>
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<td>15</td>
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<td>17</td>
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<td>18.5</td>
<td>19</td>
<td>20.5</td>
</tr>
<tr>
<td>Hb = 105 g/l</td>
<td>Amp.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5.5</td>
<td>6.5</td>
<td>9</td>
<td>9.5</td>
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<td>11</td>
<td>11.5</td>
<td>12</td>
<td>12.5</td>
<td>13</td>
<td>13.5</td>
<td>14</td>
</tr>
</tbody>
</table>

Vifor (International) Inc.,
P.O. Box, 9001 St. Gallen/Switzerland
VENOFER® PACKAGE INSERT FOR:

- BULGARIA
- CYPRUS
- ROMANIA
- RUSSIA
- SLOVAKIA
- SLOVENIA
**Venofer®**

**Therapie martiale intra-veneuse**

**COMPOSITION QUALITATIVE ET QUANTITATIVE**

1 ml contient:
- du fer sous forme de complexe d’hydruroxyde de fer(lll)-
saccharose

20 mg

**FORME PHARMACÉUTIQUE**

Solution injectable.

**DONNÉES CLINIQUES**

Indications thérapeutiques

Venofer® est indiqué dans le traitement pérénal des déficits en fer, dans les cas où la préparation orale ne suffit pas à assurer une supplémentation adéquate tels que:
- Les patients ne tolérant pas le traitement oral par les patients qui ne peuvent absorber suffisamment le traitement par voie orale.

**Posologie et mode d'administration**

**Administration**

Venofer® doit être administré par voie intraveineuse uniquement par voie intraveineuse sans dilution. Les doses administrées ne doivent pas dépasser 20 mg de fer en une injection unique. Le volume d’injectable est déterminé en fonction de la charge de fer nécessaire et de la fréquence d’administration.

**Posologie**

- En cas de malabsorption intestinale, 1 g de Venofer® peut être administré en une injection unique par voie intraveineuse.
- En cas de déficit en fer sévère, 1 g de Venofer® peut être administré en une injection unique par voie intraveineuse.

**Méthode d’administration**

- Les injections doivent être administrées par voie intraveineuse sans dilution.
- Les injections doivent être administrées par voie intraveineuse sans dilution.

**Dose**

La dose de Venofer® doit être indiquée en fonction de la charge de fer nécessaire et de la fréquence d’administration.

**Précautions**

- Les injections doivent être administrées par voie intraveineuse sans dilution.
- Les injections doivent être administrées par voie intraveineuse sans dilution.

**Conservation**

Les ampoules de Venofer® doivent être conservées hors du rayonnement et à protéger de la chaleur et de l’humidité. Les ampoules ne doivent pas être réfrigérées.

**Renseignements aux patients**

Les injections doivent être administrées par voie intraveineuse sans dilution.

**Noms commerciaux**

Venofer®

**Classe de médication**

Les médicaments contenant du fer(III) sont dans la classe des composés ferriques.

**Mécanisme d’action**

Le fer est essentiel pour la synthèse de hémoglobine et de myoglobine. Les injections de fer en intraveineuse sont utilisées pour remplacer des déficits en fer et pour prévenir les troubles de l’affinité du fer pour le corps humain.

**Contraindications**

Les injections de fer en intraveineuse ne doivent pas être administrées en cas de déficit en fer sévère.

**Effets secondaires**

Les injections de fer en intraveineuse peuvent entraîner des effets secondaires tels que des réactions allergiques, des irritations cutanées et des douleurs à l’endroit de l’injection.

**Interactions médicamenteuses**

Les injections de fer en intraveineuse peuvent interférer avec la prise de médicaments contenant du fer(III) et peuvent augmenter les risques d’effets secondaires.

**Précautions d’emploi**

Les injections de fer en intraveineuse doivent être administrées par un professionnel de santé qualifié.

**Précautions d’administration**

Les injections de fer en intraveineuse doivent être administrées par voie intraveineuse sans dilution.

**Concours**

Les injections de fer en intraveineuse sont importante pour la prévention et le traitement des déficits en fer.

**Médecins conseillers**

Les injections de fer en intraveineuse doivent être administrées par un professionnel de santé qualifié.

**Vénus**

Les injections de fer en intraveineuse sont important pour la prévention et le traitement des déficits en fer.
**Body weight / Poids corporal / Peso corporal**

<table>
<thead>
<tr>
<th></th>
<th>Kg</th>
<th>Kg</th>
<th>Kg</th>
<th>Kg</th>
<th>Kg</th>
<th>Kg</th>
<th>Kg</th>
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<th>Kg</th>
<th>Kg</th>
<th>Kg</th>
<th>Kg</th>
<th>Kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb = 60 g/l</td>
<td>72</td>
<td>64</td>
<td>57</td>
<td>52</td>
<td>48</td>
<td>44</td>
<td>40</td>
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<td>31</td>
<td>28</td>
<td>25</td>
<td>22</td>
<td>19</td>
<td>16</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Hb = 75 g/l</td>
<td>57</td>
<td>50</td>
<td>44</td>
<td>39</td>
<td>35</td>
<td>31</td>
<td>28</td>
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<td>12</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Hb = 90 g/l</td>
<td>45</td>
<td>40</td>
<td>35</td>
<td>30</td>
<td>27</td>
<td>24</td>
<td>21</td>
<td>18</td>
<td>16</td>
<td>14</td>
<td>12</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Si la dosis total necesaria supera la dosis única máxima, la administración debe ser fraccionada. Si se requiere una respuesta hematólogica sostenida, el tratamiento debe modificarse.

Cálculo de la dosis total para cada paciente de base de ferrotrast en función de la concentración de Hb.

1. **Normal pueblos:**
   - 5-10 ml de Venetrol® (100 a 200 mg de ferrotrast) cada dosis a dos veces a la semana durante el primer mes.
   - 150 mg a 2,5 ml de Venetrol® por cada día.

2. **Niños:**
   - 0.15 ml de Venetrol®/kg por día, dividido en dos partes, una a la mañana y una a la tarde.
   - 10 ml de Venetrol® (200 mg de ferrotrast) en adultos.

3. **Contraindicaciones:**
   - Alergía.
   - Enfermedades hemorragicas.
   - Trastornos sanguíneos.
   - Hepatopatía.

4. **Precauciones:**
   - No administrar a niños con antecedentes de anemia.
   - No administrar a pacientes con insuficiencia renal.
   - No administrar a pacientes con enfermedades crónicas de sangre.

5. **Interacciones:**
   - Comiendo alimentos ricos en hierro.
   - Tomando suplementos vitamínicos.

6. **Graves y reacciones adversas:**
   - Náuseas, vómitos.
   - Diarrea.
   - Hemorragias.
   - Infecciones.

7. **Instrucciones:**
   - Tomar el suplemento con una taza de agua para facilitar su absorción.
   - No tomarse más de la dosis recomendada.

**Precauciones adicionales:**

1. **Enfermedades hemolíticas:**
   - Anemia perniciosa.
   - Anemia hemolítica.
   - Anemia aplásica.

2. **Precauciones:**
   - Tomar el suplemento con una taza de agua para facilitar su absorción.
   - No tomarse más de la dosis recomendada.

**Referencias:**


**Interferencia con los análisis de laboratorio:**

1. Anemia hemolítica.
2. Anemia aplásica.
3. Anemia perniciosa.

**Precauciones:**

1. Tomar el suplemento con una taza de agua para facilitar su absorción.
2. No tomarse más de la dosis recomendada.

**Referencias:**

El texto en la imagen parece ser un fragmento de un documento médico en español. Dado que el contenido es un poco confuso y se refiere a tratamientos y efectos adversos, es posible que se trate de un cuestionario de conocimientos médicos o un resumen de un estudio científico. Sin embargo, sin el contexto completo, es difícil determinar con certeza.
Pharmacological properties
The pharmacokinetics of triodo-hydroxy-cisuroxim were investigated after intravenous injection of a single dose containing 50 mg of fentanyl in healthy volunteers. The maximum plasma levels, averaging 520 mmoles, are obtained 10 minutes after injection. The volume of distribution of the central compartment corresponds to a good agreement to the volume of xanthine (App. 3). The iron injected is quickly cleared from the system, the terminal half-life is approx. 6 h. The volume of distribution at steady state is about 2 liters, which indicates a slow iron distribution in the body water. Due to the lower stability of furoxim hydroxy-cisuroxim in comparison to the ferrous Complex, a competitive exchange of iron to transferrin was observed. This results in a low transport of approx. 33 mg Fe/Pt/ml. The renal elimination of iron, occurring in the 1st h after injection, corresponds to less than 3% of the total body clearance (approx. 20 mla/min). After 24 h of the serum levels of iron are reduced to the pre-dosage iron levels and about 75% of the dosage is excreted.

Precautionary safety data
In experimental animals toxicity was only seen at dosages which are sufficiently high in comparison to the maximum human dosage. The data from experimental animals do not show a safety risk for the human being.

PHARMACEUTICAL PARTICULARS
List of excipients
Water for injection and sodium hydroxide.

Incompatibilities
Venflax® must only be mixed with 0.9% of sodium chloride solution. No other therapeutic agent should be added.

Shelf life
See expiry date.

Special precautions for storage
Protections at a temperature of 4°C and 25°C. Protect from excessive light and do not freeze. Incorrect storage can lead to formation of sediments visible in the unsealed eye.

Nature and contents of container
Type I glass ampoules of 1 ml and extractable volume (Ph. Eutl).

Instructions for use handling
Ampoules should be thoroughly inspected for sediments and damaged before use. Only those with sediment free and homogenous solution must be used. Once opened, Venflax® should be administered immediately. Venti® diluted with 0.9% sodium chloride solution shall be limited to 12 hours if stored between 4°C and 25°C.

Package form
Ampoules (5 ml) containing 100 mg of fenc and 50 Ampoules (1 ml) containing 20 mg of fenc.

Mode of employment, Instructions concerning the manipulation
It is important to inspect the ampoules before the usual time to detect any indication of a white suspension. Even when a solution homogenous at the time of administration, certain changes which should result in immediate removal of the ampoule. The use of the ampoule should be discontinued immediately. If any solution obtained by dilution of Venflax® in NaCl 0.9% does not appear clear and homogenous in the 12 hours if it is contained between 4°C and 25°C.

Presentations
Ampoules (5 ml) containing 100 mg of fenc 5 or 50 Ampoules (1 ml) containing 20 mg of fenc 5

Propiedades farmacológicas
La administración de Venflax® se caracteriza principalmente por su eficacia en la reducción del dolor.

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