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.

/S/ 09/23/99

David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

RD Initialed by David Lee, Ph.D. /S/ 9/27/99

FT Initialed by David Lee, Ph.D. /S/ 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 I

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

**Luitpold Pharmaceuticals, Inc.**
**Iron Sucrose**
**IND #:**
**NDA #: 21-135**

| Study Number | Route of Administration | Dose (mg) | Mean Cmax ± SD | Mean Tmax (hr) | Mean Vd ± SD | Mean AUC(0-I) ± SD | Mean Kel ($hr^{-1}$) | Mean Urinary Excretion (mg) ± SD | Mean CLp (mL/min) | Mean CLr (0-24 hr) ± SD |
|---|---|---|---|---|---|---|---|---|---|---|
| **A. Vifor Pharmaceuticals, Inc. Sponsored Studies with Venofer®** | | | | | | | | | | |
| Macdougall IC et al (Report. March 5, 1999) | IV | 200 | NR | NR | NR | NR | NR | NR | NR | NR |
| Chandler G et al (Report. VIF95002, 1998) | IV | 200, 300, 400, 500 | NR | NR | NR | NR | NR | NR | NR | NR |
| Danielson B.G. et al. Internal report. 7.7.1995. *Arzneim.-Forsch./Drug Res.* 1996; 46(I); 6: | IV | 100 | 537.7 ± 106.9 µmol/L (30 mg/L) at 10 min; $C_0$: 631.2 ± 146.9µmol/L | NR | 7.3 ± 2.1L | 1491 ± 212 µmol/L/h | NR | 5.19 ± 1.28 mg /24 h | NR | 1.23 ± 0.22 /h (20.5 ± 3.7mL/min) |
| Beshara S et al (Internal Report. 14.5.1997) | IV | 100 | NR | NR | NR | NR | NR | NR | NR | NR |
| Major A et al (Report 11.3.1997) | IV | 200 | NR | NR | NR | NR | NR | NR | NR | NR |

SD: Standard deviation; NR: not reported, min: minute; mL: milliliter; µmol/L: micromolar; L: liter; mg: milligram; h: hour; IV: intravenous, $C_0$: Initial concentration, AUC: area under the curve, Cmax: maximum concentration, CLp: total body clearance, CLr: total clearance , $V_d$: volume of distribution.

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## Attachment B IN VIVO STUDY DATA SUMMARY FOR IRON SUCROSE (continued)

**Luitpold Pharmaceuticals, Inc.**
**Iron Sucrose**
**IND #: ——**
**NDA #: 21-135**

| Study Number | Route of Administration | Dose (mg) | Mean Cmax ± SD | Mean Tmax (hr) | Mean Vd ± SD | Mean AUC(0-I) ± SD | Mean Kel ($hr^{-1}$) | Mean Urinary Excretion (mg) ± SD | Mean CLp (mL/min) | Mean CLr (0-24 hr) ± SD |
|---|---|---|---|---|---|---|---|---|---|---|
| **B. Published Studies with Venofer®** | | | | | | | | | | |
| Silverberg DS et al. *Amer J Kidney Diseases*. 1996; 27(2): 234-238. | IV | 200 | NR | NR | NR | NR | NR | NR | NR | NR |
| Anatkov A. and Gekova K. *Problems of Hematology and Blood Transfusions, In Medicine and Physioculture*. 1970; 13: 295-298. | IV | 500<br><br>700-800 | 1398 ± 605 µg/dL (13.98 mg/L) at 4 h | NR | NR | NR | NR | 22.4 mg/24 h<br><br>33.7 mg/24 h | NR | NR |
| Krzysko K. et al. *Zbl. Pharm*. 1984; 123 Heft(10): 598-599. | IV | 50 | NR | NR | 0.395 ± 0.117 L/kg | 24,324 ± 15,644 µg/h/mL | NR | NR | NR | 0.074 ± 0.086 L/h/kg |
| Al-Momem A.K. et al. *Saudi J. Kidney Dis. Transplant*. 1994; 5(2): 168-172. | IV | 100, 500 | NR | NR | NR | NR | NR | NR | NR | NR |

NR: Not reported, min: minute; mL: milliliter; µmol/L: micromolar; L: liter; mg: milligram; h: hour; IV: intravenous, $C_o$: Initial concentration, AUC: area under the curve, Cmax: maximum concentration, CLp: total body clearance, CLr: total clearance , $V_d$: volume of distribution, SD: standard deviation.



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## 6.3 Tabulated Summaries of Bioavailability and Pharmacokinetic Studies

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

| Name of Company: Luitpold Pharmaceuticals, Inc.<br>Name of Finished Product: Venofer®<br>Name of Active substance(s): Iron Sucrose | BIOPHARMACEUTICS STUDY SUMMARY<br>BIOAVAILABILITY STUDIES: RELEASE OF IRON TO TRANSFERRIN IRON POOL (200 MG IRON [Fe]) | IND #: ——<br>SUBMISSION DATE: October 15, 1998 |
|---|---|---|

| Ref. | Study Investigator -Co-ordinating Center(s) | Design | Number of Subjects, Sex, and Age | Diagnosis and Criteria for Inclusion | Duration of Treatment | Test Product Dosage Regimen Route of Administration | Reference Therapy Dose Regimen Route of Administration | Criteria for Evaluation | Results | Safety |
|---|---|---|---|---|---|---|---|---|---|---|
| Att.1 Section 6 | Internal Report CT104; March 5, 1999<br>-Macdougall IC, Chandler, G, Armstrong A, Breen C, Harchowal J, Cavill I.<br><br>-Department of Renal Medicine, King's College, London, UK | Single-center, randomized, open, parallel, comparative | N=60<br>Group A=20<br>Group B=20<br>Group C=20<br><br>Group A:<br>Mean age 58 years<br>13 males<br>7 females<br><br>Group B:<br>Mean age 63 years<br>12 males<br>8 females<br><br>Group C:<br>Mean age 60 years<br>11 males<br>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, 1/4, 1/2, 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 dextrin) 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 dextrin (Group A) and iron sucrose (Group C), but three anaphylactic reactions with iron dextran (Group B). |

N: number, mg: milligram, IV: intravenous.



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## Table 3 Bioavailability Studies: Effects of Erythropoietin With and Without Iron Sucrose Treatment on Reticulocyte Response

| Name of Company: Luitpold Pharmaceuticals, Inc. Name of Finished Product: Venofer® Name of Active substance(s): Iron Sucrose | BIOPHARMACEUTICS STUDY SUMMARY<br>BIOAVAILABILITY STUDIES: EFFECTS OF ERYTHROPOIETIN WITH AND WITHOUT IRON SUCROSE TREATMENT ON RETICULOCYTE RESPONSE | IND #: —<br>SUBMISSION DATE: October 15, 1998 |
|---|---|---|

| Ref. | Study<br>Investigator<br>Co-ordinating Center(s) | Design | Number of Subjects, Sex, and Age | Diagnosis and Criteria for Inclusion | Duration of Treatment | Test Product Dosage Regimen Route of Administration/Rate of Infusion | Reference Therapy Dose Regimen Route of Administration | Criteria for Evaluation | Results | Safety |
|---|---|---|---|---|---|---|---|---|---|---|
| Att. 2 Section 6 | Study Report, 11.3.1997. Brit. J. of Haematology. 1997; 98: 292-294.<br>-Major A, Mathez-Loic F, Rohling R, Gautschi K, Brugnara C.<br>-University Hospital, Department of Obstetrics and Gynecology, Zurich, Switzerland | Controlled, randomized, parallel group comparative | N=14<br>Group A=7<br>Group B=7<br>Age<br>21-36 years<br>6 males<br>8 females | Healthy adult volunteers | Single application, observation time=8 days | Group A:<br>300 IU/kg IV r-HuEPO<br>+<br>200 mg iron sucrose (Venofer®)<br>Rate: NR | Group B:<br>300 IU/kg r-HuEPO IV | Red cell and reticulocyte indices, hemoglobin content of reticulocytes, absolute reticulocyte count, young and old reticulocytes, serum EPO, and serum ferritin concentration. | The concomitant administration of iron sucrose significantly increases the hemopoietic response to r-HuEPO in normal subjects. | No adverse events reported. |

NR; Not reported, N; number, IV: intravenous, kg: kilogram, IU: international units.

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## Table 4 Human Pharmacokinetic Studies: Pharmacokinetics of a Single 100 Mg Dose of Iron Sucrose

| Name of Company: Luitpold Pharmaceuticals, Inc. Name of Finished Product: Venofer® Name of Active substance(s): Iron Sucrose | BIOPHARMACEUTICS STUDY SUMMARY<br>HUMAN PHARMACOKINETIC STUDIES: PHARMACOKINETICS OF A SINGLE 100 MG DOSE OF IRON SUCROSE | IND #: —<br>SUBMISSION DATE: October 15, 1998 |
|---|---|---|

| Ref. | Study<br>-Investigator<br>-Co-ordinating Center(s) | Design | Number of Subjects, Sex, and Age | Diagnosis and Criteria for Inclusion | Duration of Treatment | Test Product Dosage Regimen Route of Administration | Criteria for Evaluation | Results | Safety |
|---|---|---|---|---|---|---|---|---|---|
| Att. 3 Section 6 | Internal report. 7.7.1995. Arzneim.-Forsch./Drug Res. 1996; 46(I); 6: 615-621.<br><br>-Danielson BG, Salmonson T, Derendorf H, Geisser P.<br><br>-Department of Medicine, University Hospital, Uppsala, Sweden | Open, single dose | N=12<br><br>3 males<br>9 females<br><br>35-50 years | Adult healthy subjects | Single application | Iron sucrose (Venofer®) 100 mg iron | Hematological parameters, serum iron, serum transferrin, ferritin, urinary iron and sucrose, AUC, AUMC, MRT, CL, $V_c$, $Vd_{ss}$, $Vd_{area}$, and $t_{1/2}$ | There was no statistically significant difference in serum iron levels before and 24 hours after injection.<br><br>Terminal half-life ≥ 6 hours. Renal elimination of iron was low (<5%) primarily during 4 hours after injection. Seventy-five percent of the dose of sucrose was excreted in urine during 24 hours. No increase in serum transferrin levels. Serum ferritin levels increased after 8-10 hours and doubled by 24 hours. | No adverse reactions reported. |

N: number, mg: milligram; AUC: area under the curve, AUMC: area under mean curve, MRT: mean residence time, CL: , $V_c$: volume of distribution of the central compartment, $Vd_{ss}$: volume of distribution at steady state, $Vd_{area}$: volume of distribution during elimination, $t_{1/2}$: terminal half life.

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## Table 5 Human Pharmacokinetic Study: Pharmacokinetics of Radiolabeled Iron-Sucrose

| Name of Company: Luitpold Pharmaceuticals, Inc.<br>Name of Finished Product: Venofer®<br>Name of Active substance(s): Iron Sucrose | BIOPHARMACEUTICS STUDY SUMMARY<br>HUMAN PHARMACOKINETIC STUDIES: PHARMACOKINETICS OF RADIOLABELED IRON-SUCROSE | IND #: —<br>SUBMISSION DATE: October 15, 1998 |
|---|---|---|

| Ref. | Study<br>- Investigator<br>- Co-ordinating Center(s) | Design | Number of Subjects, Sex, and Age | Diagnosis and Criteria for Inclusion | Duration of Treatment | Test Product Dosage Regimen Route of Administration | Reference Therapy Dose Regimen Route of Administration | Criteria for Evaluation | Results | Safety |
|---|---|---|---|---|---|---|---|---|---|---|
| Att. 4 Section 6 | Zbl. Pharm. 1984; 123 Heft(10): 598-599.<br><br>-Krzysko K, Bokowski W, Wichlinski LM.<br><br>-Dept. of Biopharmaceutics Faculty of Pharmacy Bydgoszcz, Poland | Open, cross-over | N=11<br><br>Sex=NR<br><br>Age=NR | Healthy subjects | Single bolus injection | Iron sucrose 2.5 mL (50 mg iron) given intravenously | Hemofer® prolongatum 210 mg oral iron as ferrous fumarate | Pharmacokinetic parameters after IV administration and bioavailability after oral administration | Half-life time of serum iron was 9.31 ± 6.77 hours. Iron was mainly distributed in intracellular space. Plasma clearance of 0.074 $dm^3/h/kg$ | NR |

NR: Not reported, mL: milliliter, N: number, mg: milligram, kg: kilogram, h: hour.

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## Table 6 Human Pharmacokinetic Studies: Red Cell Utilization of Radiolabeled Iron Sucrose

| Name of Company: Luitpold Pharmaceuticals, Inc.<br>Name of Finished Product: Venofer®<br>Name of Active substance(s): Iron Sucrose | BIOPHARMACEUTICS STUDY SUMMARY<br>HUMAN PHARMACOKINETIC STUDIES: RED CELL UTILIZATION OF RADIOLABELED IRON SUCROSE | IND #: —<br>SUBMISSION DATE: October 15, 1998 |
|---|---|---|

| Ref. | Study<br>- Investigator<br>- Co-ordinating Center(s) | Design | Number of Subjects, Sex, and Age | Diagnosis and Criteria for Inclusion | Duration of Treatment | Test Product Dosage Regimen Route of Administration | Criteria for Evaluation | Results | Safety |
|---|---|---|---|---|---|---|---|---|---|
| Att. 5 Section 6 | Internal report. 14.5.1997<br>-Beshara S, Lundqvist H, Sundin J, et al.<br><br>-Department of Internal Medicine, University Hospital, Uppsala, Sweden | Open | N=6<br><br>2 males<br>4 females<br><br>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®) ($^{52}Fe/^{59}Fe$ radio-labeled) | Distribution and incorporation of labeled iron: emission scans performed for $^{52}Fe$ 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%.<br>Iron deficiency: 88% and 94%<br>Renal anemia: 76% and 97%<br>Functional iron deficiency: 68% and 76% | No adverse events observed. |

N: number, ml: milliliter, mg: milligram, IV: intravenous.

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## Table 7 Human Pharmacokinetic Studies: Serum Iron Levels and Urinary Excretion

| Name of Company: Luitpold Pharmaceuticals, Inc. Name of Finished Product: Venofer® Name of Active substance(s): Iron Sucrose | BIOPHARMACEUTICS STUDY SUMMARY HUMAN PHARMACOKINETIC STUDIES: SERUM IRON LEVELS AND URINARY EXCRETION | IND #: — SUBMISSION DATE: October 15, 1998 |
|---|---|---|

| Ref. | Study - Investigator - Co-ordinating Center(s) | Design | Number of Subjects, Sex, and Age | Diagnosis and Criteria for Inclusion | Duration of Treatment | Test Product Dosage Regimen Route of Administration | Criteria for Evaluation | Results | Safety |
|---|---|---|---|---|---|---|---|---|---|
| All 6 Section 6 | Problems of Hematology and Blood Transfusions, in Medicine and Physioculture. 1970; 13: 295-298 -Anatkov A, Gekova K. - NR | Open, non-controlled | N=26 3 males 23 females 16-60 years | Iron deficiency anemia caused by achlorhydria, menorrhagia, miscellaneous, and gastric resection | 3 days | 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 | Changes in hematological parameters and urinary estimation of iron | 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. | Mild headache and nausea 500 mg iron in 7.8% 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. |

NR: Not reported, N: number, IV: intravenous, mg: milligram.

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## 6.4 Summary of Bioavailability/Bioequivalence Studies

### 6.4.1 Bioavailability Studies in Dialysis Patients With Anemia.

Macdougall IC, Chandler G, Armstrong A, Breen C, Harchowal J, and Cavill I. Characterisation of iron availability from three different IV iron preparations in dialysis patients. Internal Report CT104; March 5, 1999. Abstract from the 30th Annual Meeting and Scientific Exposition of the American Society of Nephrology. November 2-5, 1997, San Antonio, Texas, U.S.A.

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.

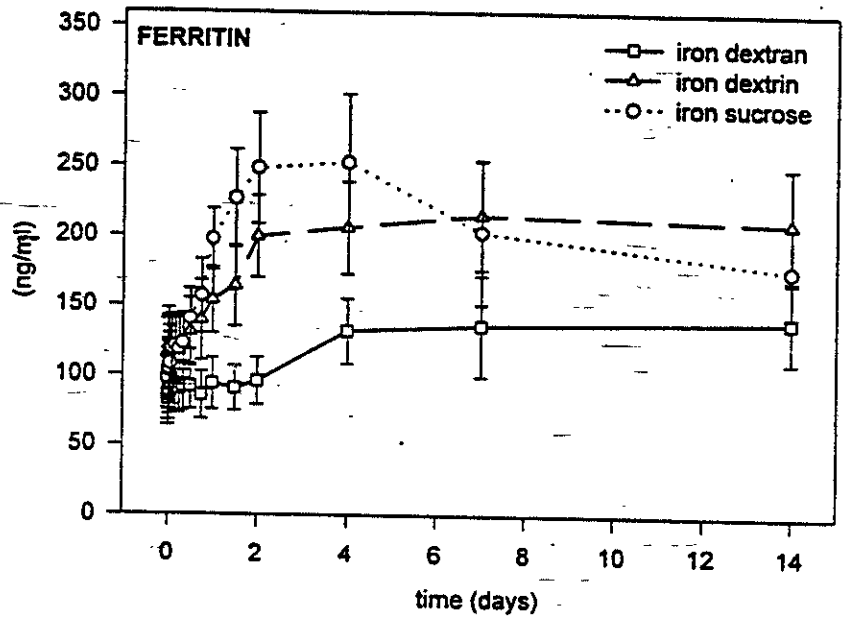
- At 0, ¼, ½, 1, 2, 4, 6, 8, 12, 18, 24, 36 and 48 hours after injection the following were measured: serum iron, serum total iron binding capacity (TIBC), transferrin saturation, and total circulating iron.

- 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.

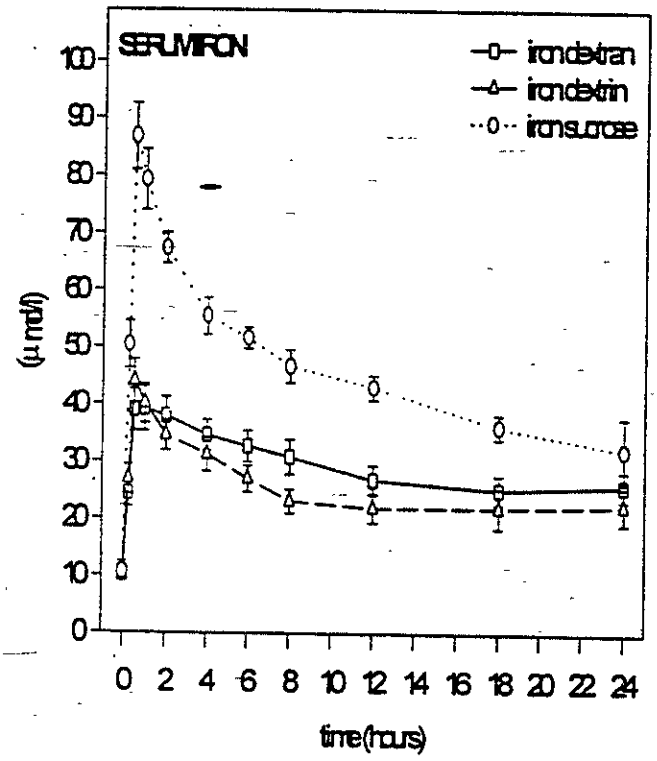
**Table 8** **Serum Iron Levels 30 Minutes After IV Administration of Three Different Iron Preparations**

| | Form of Iron Delivery (200 Mg Iron) | | |
|---|---|---|---|
| | Iron Sucrose | Iron Dextrin | Iron Dextran |
| Number of Patients | 20 | 20 | 20 |
| Serum Iron | 87±22 µmol/L†* | 44±15 µmol/L | 39±13 µmol/L |

† Values are means±standard errors.
*P<0.01 compared to iron dextrin and iron dextran.
µmol/L: micromolar.

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)**



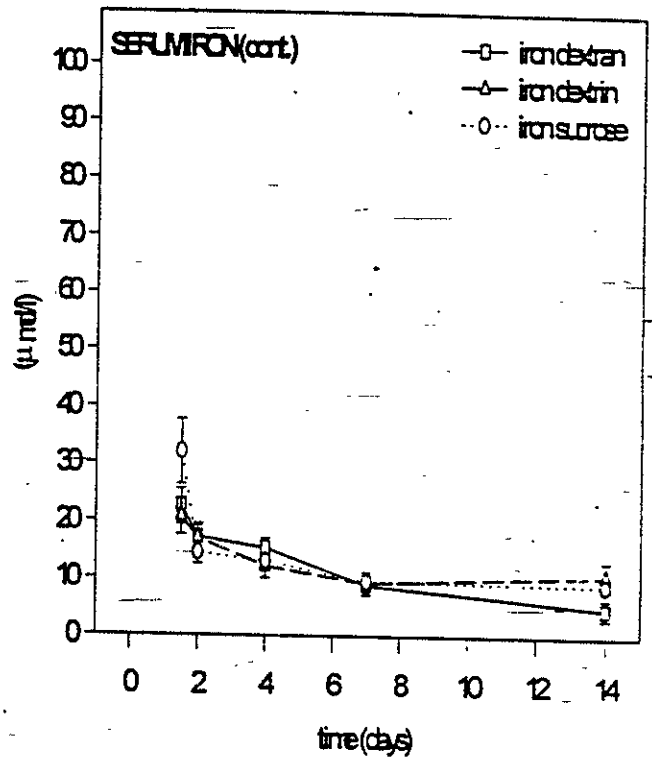




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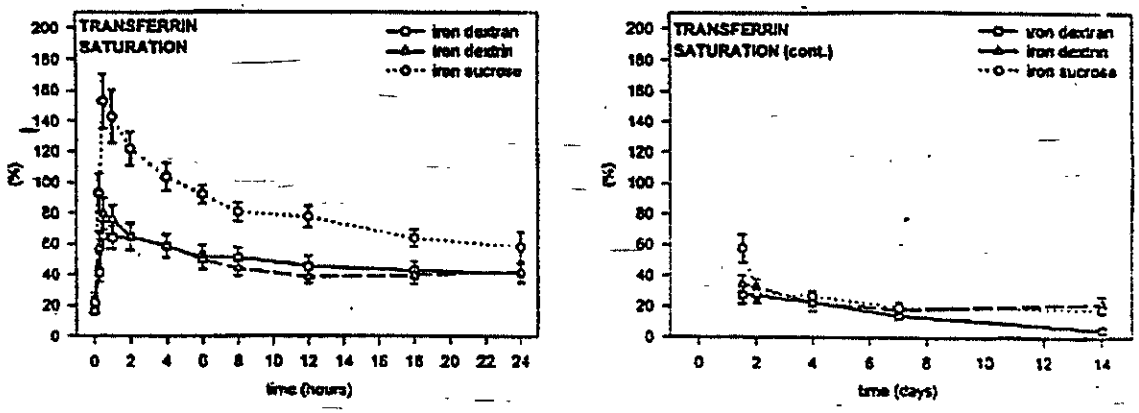
Figure 3 shows that peak percent transferrin saturation was higher in patients receiving iron sucrose than in patients receiving other iron formulations. Transferrin saturation values peaked at 30 minutes-1 hour at >100% with iron sucrose and they gradually fell to baseline values over the next 24 hours.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

Major A et al. The effect of intravenous iron on the reticulocyte response to recombinant human erythropoietin. Study Report, Zurich 11.3.1997. *Brit J of Haematology*. 1997; 98: 292-294.

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**

| | Reticulocyte CHr (pg) † | | Serum Ferritin (µg/L) † | |
|---|---|---|---|---|
| Time | Control | Iron Sucrose | Control | Iron Sucrose |
| Baseline | 31.8±0.9 | 32.5±1.3 | 77±71.3 | 83.7±62.4 |
| Day 1 | 32.1±1.2 | 33±1.5 | 72.6±68.3 | 162.6±61.7* |
| Day 2 | 31.4±0.9 | 32.6±1.1* | 58.7±56.1 | 162.8±51.9* |
| Day 3 | 31.5±1.5 | 33.5±1.2* | 39.3±40.3 | 138.7±52.8* |
| Day 4 | 32.8±1.8 | 35±1.1* | 42.8±42 | 121±32.7* |
| Day 6 | 31±2 | 33.4±1.6* | 37.7±37.6 | 92.7±33.9* |
| Day 7 | 30.6±1.7 | 32.9±2.1* | 43.8±40.6 | 100.4±40* |
| Day 8 | 30.7±1.7 | 32.9±1.9* | 47.4±50 | 109.4±46.9* |

* Mann-Whitney U-test p<0.05 compared with controls.
† Results expressed as mean ± standard deviation.
ug/L: microgram per liter.

**Figure 4** **Reticulocyte Hemoglobin and Hemoglobin Content of Young and Old Reticulocytes (CHyoung R and CHold R) in Subjects Receiving Erythropoietin Alone ("Control"), and Erythropoietin and Iron Sucrose**

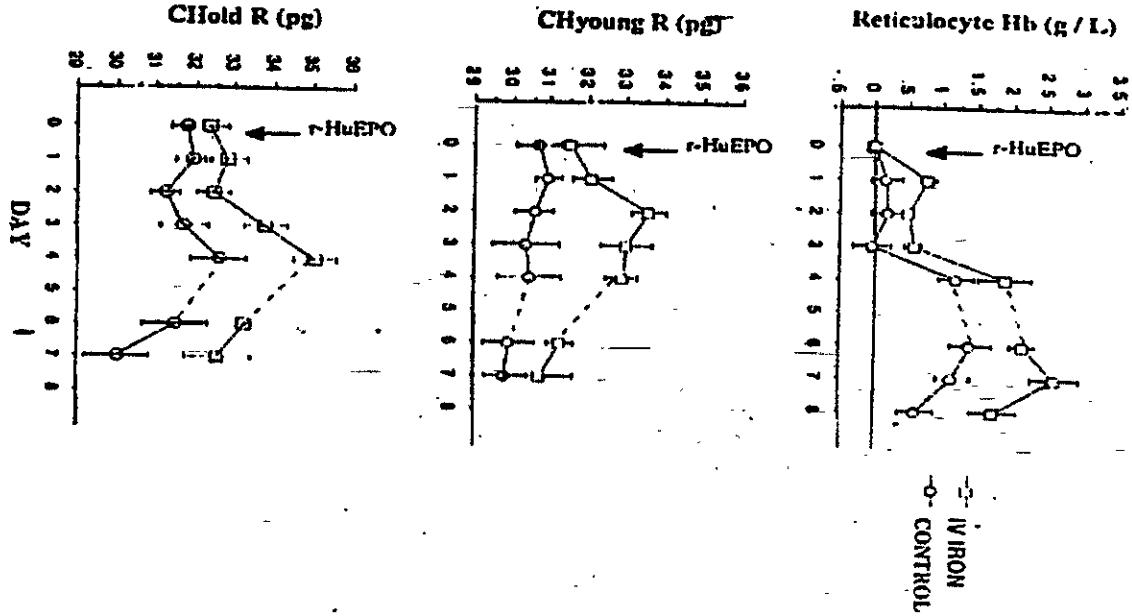



Table 9 and Figure 4 show that CHr was significantly higher in the iron sucrose + r-HuEPO patients (Group A) from day 3 onward compared with the r-HuEPO patients (Group B).

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 BG et al. Pharmacokinetics of iron (III)-hydroxide sucrose complex (Venofer®) after single IV dose in healthy volunteers. Internal report. 7.7.1995. *Arzneim.-Forsch./Drug Res.* 1996; 46(I); 6: 615-621.

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 Venofer®). 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 10 Pharmacokinetic Parameters After Single Intravenous Administration of 100 mg Iron as Iron Sucrose (Venofer®)**

| | Method of Analysis | | |
|---|---|---|---|
| Parameters | Non-Compartmental | Compartmental | Michaelis Menten |
| $C_{max}$ $(C_0)^{@}$ (µmol/L) | 584 | 607 | 631±146.9 |
| $T_{1/2\beta}$ (hours) | 7.0 | 6.3 | 5.3±1.6 |
| MRT † (hours) | 8.2 | 7.1 | 5.5±1.2 |
| AUC (µmol/L h) | 1680 | 1553 | 1491±212 |
| Total body clearance (mL/min) (L/h) | 18.5 | 20.0 | 20.5±3.7 1.23±0.22 |
| $V_c$ (Liters) | 3.3 | 3.1 | 3.2±0.7 |
| $Vd_{ss}$ ‡ (Liters) | 8.4 | 7.9 | 7.3±2.1 |
| Vd area** | 10.4 | 10.1 | 9.2±2.3 |
| Transferrin mg Fe/24 h†† | - | - | 31.0±6.6 |

@ $C_0$: Calculated initial concentration
†MRT: Mean residence time
‡$Vd_{ss}$: Volume of distribution at steady state.
*$V_c$: Volume of distribution of the central compartment.
**Vd: Volume of distribution during elimination.
††: Calculated amount of iron transported by transferrin.
µmol/L: micromolar.
$T_{1/2}$: 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 $^{59}$Fe-labeled Iron Sucrose

Krzysko K et al. Pharmacokinetics of serum iron in humans. *Zbl. Pharm.* 1984; 123 Heft(10): 598-599.

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 11 Selected Pharmacokinetic Parameters Following Intravenous Administration of 50 Mg Iron as Iron Sucrose**

| Parameters | Units | Mean±SD |
|---|---|---|
| Initial Phase Constant (A) | µg/mL | 1.635±0.758 |
| Initial Phase Constant (B) | µg/mL | 2.015±0.464 |
| Fast Phase Constant (α) | $h^{-1}$ | 2.514±1.612 |
| Slow phase constant (β) | $h^{-1}$ | 0.104±0.057 |
| Blood→tissue distribution value ($\kappa_{12}$) | $h^{-1}$ | 1.230±0.836 |
| Tissue→blood distribution value ($\kappa_{21}$) | $h^{-1}$ | 1.151±0.811 |
| Low value of distribution volume of central compartment ($\Lambda_1'$) | $dm^3/kg$ | 0.223±0.068 |
| Total clearance of iron ($\Lambda'K$) | $dm^3\ h^{-1}kg^{-1}$ | 0.074±0.086 |
| Overall distribution coefficient ($\Lambda'$area) | $dm^3/kg$ | 0.395±0.117 |
| Half-life | Hours | 9.31±6.77 |
| Fraction of dose absorbed (F') | % | 6.65±4.91 |

µg/mL: microgram per milliliters, kg: kilogram, h: hour.

### 6.5.3 Ferrokinetics Evaluated by Positron Emission Tomography

Beshara S, Lundqvist H, Sundin J, et al. Pharmacokinetic analysis and red cell utilization of $^{52}Fe/^{59}Fe$-labeled iron (III)-hydroxide sucrose complex following intravenous administration using positron emission tomography (PET). Study in patients with iron deficiency and renal anemia. Internal report. 14.5.1997. Beshara S, Lundqvist H, Sundin J et al. Kinetic analysis of $^{52}Fe$ -labelled iron(III) hydroxide-sucrose complex following bolus administration using positron emission tomography. *Brit. J. of Haematology*. 1999; 104: 288-295.

Beshara et al. (1997)[5] performed an open study of the pharmacokinetics and red cell utilization of $^{52}Fe/^{59}Fe$-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**

| Patient 1 | | Patient 2 | | Patient 3 | | Patient 4* | | Patient 5 | | Patient 6 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | % | Day | % | Day | % | Day | % | Day | % | Day | % |
| 1 | 5 | 1 | 9 | 1 | 1 | 1 | - | 1 | 5 | 1 | 3 |
| 2 | 21 | 2 | 14 | 2 | 6 | 2 | 10 | 2 | 15 | 2 | 8 |
| 3 | 52 | 3 | 29 | 3 | 18 | 3 | 10 | 9 | 78 | 6 | 52 |
| 6 | 64 | 6 | 66 | 6 | 43 | 6 | 73 | 13 | 81 | 8 | 58 |
| 9 | 62 | 9 | 88 | 9 | 56 | 23 | 46 | 16 | 83 | 13 | 68 |
| 13 | 69 | 13 | 90 | 13 | 62 | 28 | 76 | 20 | 85 | 15 | 76 |
| 16 | 91 | 16 | 87 | 15 | 59 | - | - | 23 | 86 | 19 | 71 |
| 20 | 82 | 21 | 86 | 21 | 66 | - | - | 27 | 88 | 22 | 72 |
| 23 | 97 | 24 | 94 | 24 | 68 | - | - | - | - | - | - |
| - | - | 28 | 89 | 28 | 64 | - | - | - | - | - | - |

*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 $^{52}Fe/^{59}Fe$-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 $^{52}Fe/^{59}Fe$-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 A and Gekova K. The use of large intravenous doses of iron in the treatment of iron-deficiency anemia. *Problems of Hematology and Blood Transfusions, in Medicine and Physioculture*. 1970; 13: 295-298 (translation).

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**

| | Baseline Value | Average Change in Hemoglobin at 2, 4, and 6 Weeks After Administration of Iron Sucrose | | |
|---|---|---|---|---|
| | | 2 | 4 | 6 |
| Change from Baseline in Hb (g/dL) | 6.2±1.13 | +1.35* | +0.7* | +0.35* |

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**

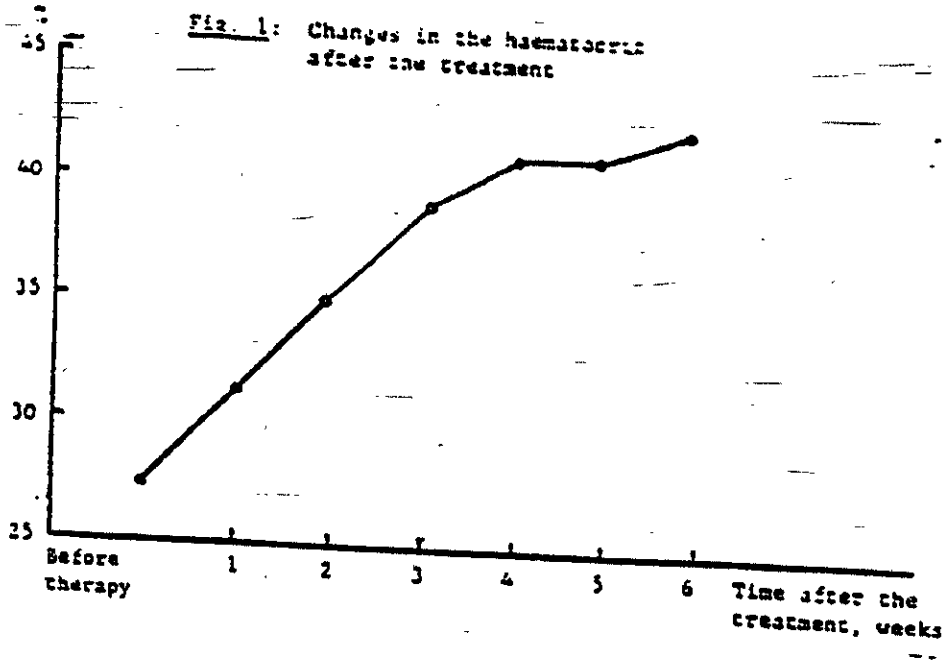



**Table 14 Mean Values for Serum Iron at Baseline and Weeks 5 and 8 Following IV Administration of Iron Sucrose**

| Parameter | Baseline Value | Values At Weeks 5 and 8 After IV Iron Sucrose | |
|---|---|---|---|
| | | 5 | 8 |
| Serum Iron (µg/dL) | 35 ± 18.1 | 98 ± 38.4 | 116# |
| TIBC (µg) | 522 ± 71.8 | 392 ± 38.4 | 354 ± 17.8 |

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

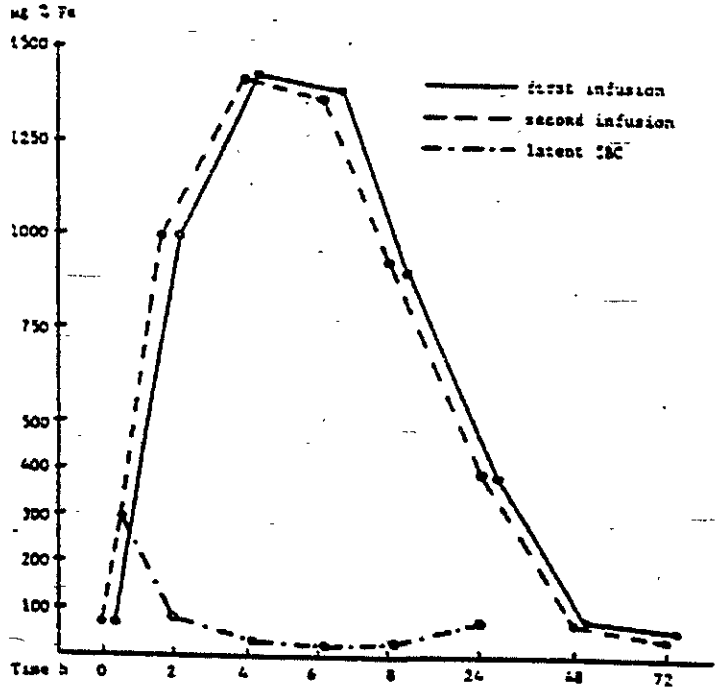
following a single intravenous dose of 500-800 mg iron sucrose which decreased to near baseline values within 48 hours.

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

| | Serum Iron Levels (µg/dL) | |
|---|---|---|
| | First Infusion | Second Infusion |
| **Time of Measure** | | |
| 4 Hours | 1398 ± 605 | 1498 ± 692 |
| 24 Hours | 440 ± 218 | 428 ± 228 |
| 48 Hours | 103 ± 41 | 114 ± 51 |
| 72 Hours | 77 | 94 |

µg: microgram, dL: deciliter.

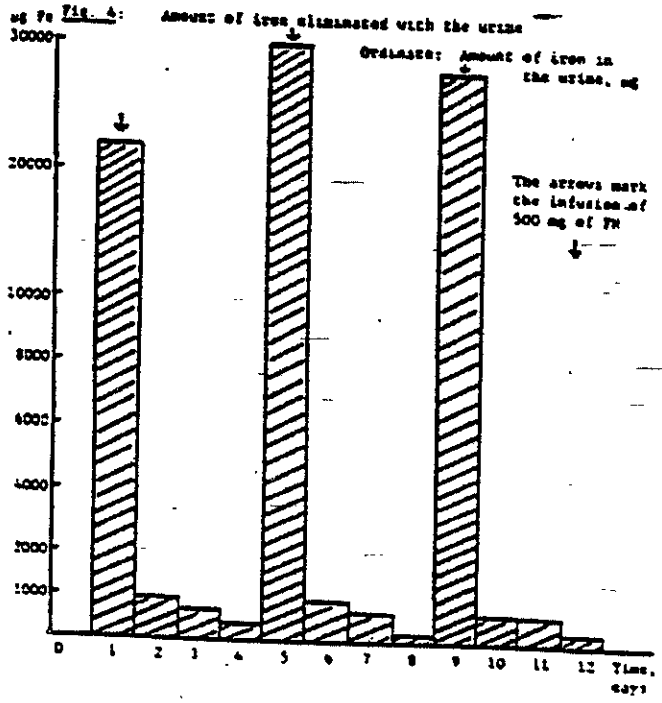
**Figure 6 Serum Iron Level During and After the Infusion of 500 Mg of Iron Sucrose**




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.

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## 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

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## Table 16 Other *In Vivo* Studies: Dose-Tolerance Study

| Name of Company: Luitpold Pharmaceuticals, Inc. Name of Finished Product: Venofer® Name of Active substance(s): Iron Sucrose | BIOPHARMACEUTICS STUDY SUMMARY OTHER *IN VIVO* STUDIES: DOSE-TOLERANCE STUDY | IND #: ⟶ SUBMISSION DATE: |
|---|---|---|

| Ref. | Study -Investigator -Co-ordinating Center(s) | Design | Number of Subjects, Sex, and Age | Diagnosis and Criteria for Inclusion | Duration of Treatment | Test Product Dosage Regimen Route of Administration | Criteria for Evaluation | Results | Safety |
|---|---|---|---|---|---|---|---|---|---|
| Att. 7 Section 6 | Internal Report. VIF95002, 1998 -Chandler G, Harchowal J, Macdougall IC. -Department of Renal Medicine and Pharmacy, King's College Hospital, London, UK | Uncontrolled, dose range finding with regard to tolerability | N=335 200 mg=89 300 mg=189 400 mg=35 500 mg=22 175 males 160 females Age 22-82 years | Anemic patients (hemodialysis, CAPD, pre-dialysis, and transplant patients) | Single dose | 200 mg, 300 mg, 400 mg, and 500 mg of IV iron (as iron sucrose, Venofer®) given within 2 hours | Safety variables | The results demonstrate the safety and tolerance of iron sucrose at doses of 200 mg and 300 mg infused over 2 hours. The higher doses (400 mg and 500 mg over 2 hours) lead to a transient iron-overload, which might be responsible for hypotension and other adverse drug reactions. Duration of the infusion should be increased with higher iron doses, ie , to administer 400 mg of iron over 2.5 hours and 500 mg over 3.5 hours. | Good tolerance of IV iron sucrose at doses of 200 mg and 300 mg. Adverse events reported at doses of 400 mg and 500 mg were 6% and 36%, respectively. Iron sucrose was infused much faster than recommended by the manufacturer. Two patients receiving 400 mg and eight patients receiving 500 mg experienced hypotension (9) accompanied by nausea (5), vomiting (3), lower back pain (2), back pain (1), and bilateral edema of hands and feet (1). Three hypotensive patients were hospitalized. |

N: number, mg: milligram, IV: intravenous.

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## Table 17 Other *In Vivo* Studies: Intravenous Iron Sucrose Versus Oral Iron and Erythropoietin

| Name of Company: Luitpold Pharmaceuticals, Inc. Name of Finished Product: Venofer® Name of Active substance(s): Iron Sucrose | BIOPHARMACEUTICS STUDY SUMMARY OTHER *IN VIVO* STUDIES: INTRAVENOUS IRON SUCROSE VERSUS ORAL IRON AND ERYTHROPOIETIN | | | | | | | IND #: — SUBMISSION DATE: October 15, 1998 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Ref. | Study -Investigator -Co-ordinating Center(s) | Design | Number of Subjects, Sex, and Age | Diagnosis and Criteria for Inclusion | Duration of Treatment | Test Product Dosage Regimen Route of Administration | Reference Therapy Dose Regimen Route of Administration | Criteria for Evaluation | Results | Safety |
| Att. 8 Section 6 | Internal report. 1993a. -Danielson, B. -Dept. of Medicine University Hospital, Uppsala, Sweden | Open comparative | N=23[a] Group 1=20 Group 2=3 13 males 10 females 50-79 years[b] mean 54 years[b] | 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. |

a: These patients are a subset of the 110 patients included in Ref. 9, Danielson, 1993b.
b: Age range and mean for 20 patients in Group 1.
N: number, mg: milligram, IV: intravenous.

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## Table 18 Other *In Vivo* Studies: Efficacy and Tolerance Study in Dialysis Patients Receiving Erythropoietin

| Name of Company: Luitpold P..armaceuticals, Inc.<br>Name of Finished Product: Venofer®<br>Name of Active substance(s): Iron Sucrose | | | | BIOPHARMACEUTICS STUDY SUMMARY<br>OTHER *IN VIVO* STUDIES: EFFICACY AND TOLERANCE STUDY IN DIALYSIS PATIENTS RECEIVING ERYTHROPOIETIN | | | IND #: —<br>SUBMISSION DATE: October 15, 1998 | | |
|---|---|---|---|---|---|---|---|---|---|
| Ref. | Study<br>-Investigator<br>-Co-ordinating Center(s) | Design | Number of Subjects, Sex, and Age | Diagnosis and Criteria for Inclusion | Duration of Treatment | Test Product Dosage Regimen<br>Route of Administration | Criteria for Evaluation | Results | Safety |
| Att. 9<br>Section 6 | Internal report. 1993b.<br>-Danielson BG<br><br>-Department of Medicine University Hospital, Uppsala, Sweden | Open | N=110 [a]<br><br>61 males<br>49 females<br><br>Age range at start of treatment: 57-92 | Anemic patients with chronic renal failure treated with r-HuEPO | Up to 48 months<br>Mean=12 months | Iron sucrose: test dose=50 mg iron IV/2-5 minutes<br><br>Treatment dose: 50-100 mg iron 1-3 times/week/post-dialysis<br>Mean dose: 180 mg/week/serum ferritin kept at range of 200-800 µg/L<br><br>Average maintenance dose: 180 mg iron/week | Hematological parameters, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, serum iron, transferrin, ferritin, and all safety variables | Iron stores were effectively and promptly replenished. | Four patients experienced adverse effects:<br>one transient metallic taste which stopped when infusion rate was extended to 3-5 minutes;<br>one female with GI-symptoms, including vomiting and nausea and patient was discontinued from IV iron; one male with fever was withdrawn;<br>one male with exanthema on the arms, legs and trunk without anaphylactoid reaction was withdrawn. |

A: Pharmacokinetic results for 20 patients also presented. See Danielson 1993a for results.
N: number, mg: milligram, IV: intravenous.

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## Table 19 Other *In Vivo* Studies: High and Low Dose Intravenous Iron Sucrose in Patients With and Without Iron Deficiency

| Name of Company: Luitpold Pharmaceuticals, Inc. Name of Finished Product: Venofer® Name of Active substance(s): Iron Sucrose | BIOPHARMACEUTICS STUDY SUMMARY OTHER *IN VIVO* STUDIES: HIGH AND LOW DOSE INTRAVENOUS IRON SUCROSE IN PATIENTS WITH AND WITHOUT IRON DEFICIENCY | | | | | | | IND #: —— SUBMISSION DATE: October 15, 1998 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Ref. | Study -Investigator -Co-ordinating Center(s) | Design | Number of Subjects, Sex, and Age | Diagnosis and Criteria for Inclusion | Duration of Treatment | Test Product Dosage Regimen Route of Administration | Reference Therapy Dose Regimen Route of Administration | Criteria for Evaluation | Results | Safety |
| Att. 10 Section 6 | *Saudi J Kidney Dis Transplant.* 1994; 5(2): 168-172.<br><br>-Al-Momen AK, Huraib SO, Mitwalli AH, et al.<br><br>-College of Medicine and King Khalid University Hospital Riyadh, Saudi Arabia | Open, dosage comparison | N=109<br>high dose=58<br>low dose=51<br><br>57 males<br>52 females<br><br>34.1 ± 11.7 years (range 17-65 years) | Hemodialysis patients on r-HuEPO for 8 weeks or longer<br><br>64 were iron-deficient | To a calculated dose for high dose; 2-3 weeks for low dose<br><br>Analyses performed at 4 weeks | High dose: iron sucrose 500 mg iron IV over 1-4 hours once weekly up to the calculated dose | Low dose: iron sucrose 100 mg iron IV over 5-10 minutes 3x/week Total dose: 500-1000 mg iron | Changes in hematological parameters, serum iron, ferritin, and hematocrit | 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. | 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.<br><br>Low dose: No adverse reactions |

N: number, mg: milligram, IV: intravenous.

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## Table 20 Human Pharmacokinetic Studies: Long-Term Effects of Intravenous Iron Sucrose Complex Treatment

| Name of Company: Luitpold Pharmaceuticals, Inc. Name of Finished Product: Venofer® Name of Active substance(s): Iron Sucrose | BIOPHARMACEUTICS STUDY SUMMARY<br>HUMAN PHARMACOKINETIC STUDIES: LONG-TERM EFFECTS OF INTRAVENOUS IRON SUCROSE COMPLEX TREATMENT | IND #: —<br>DATE OF SUBMISSION: October 15, 1998 | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Ref.** | **Study**<br>- Investigator<br>- Co-ordinating Center(s) | **Design** | **Number of Subjects, Sex, and Age** | **Diagnosis and Criteria for Inclusion** | **Duration of Treatment** | **Test Product Dosage Regimen Route of Administration** | **Criteria for Evaluation** | **Results** | **Safety** |
| Att. 11 Section 6 | *Amer. J. Kidney Diseases* 1996; 27(2):234-238. -Silverberg DS, Iaina A, Peer G, *et al.*<br><br>-Department Nephrology Ichilvov Hospital Tel Aviv, Israel | Open | N=34[a]<br><br>18 males<br>15 females<br><br>Age<br>27-74 years | Anemic patients with moderate to severe chronic renal failure (creatinine clearance 10-40 mL/min) and hemoglobin <11.0 g/dL | 5 months | Iron sucrose, 200 mg iron IV in 150 mL saline over 2 hours once monthly for 5 months<br><br>Total dose=1000 mg iron<br><br>Test dose: 25 mg iron IV in 100 mL saline over 1 hour. | Serum creatinine, complete blood count, serum ferritin, serum iron, total iron-binding capacity, creatinine clearance every 3 and 6 months, and serum iron saturation | 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. | 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. |

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

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### 6.6.2 Dose-Tolerance Study in Dialysis Patients With Anemia

Chandler G, Harchowal J, and Macdougall I . Intravenous iron (III)-hydroxide sucrose complex: Establishing the optimum dose given as an infusion over two hours. Internal Report. VIF95002, 1998. Abstract from the 30th Annual Meeting and Scientific Exposition of the American Society of Nephrology. November 2-5, 1997, San Antonio, Texas, U.S.A.

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**

| Iron Sucrose Dose | Number of Patients | Number and Percent with Reactions |
|---|---|---|
| 200 mg iron | 89 | 0 ( 0%) |
| 300 mg iron | 189 | 0 ( 0%) |
| 400 mg iron | 35 | 2 ( 6%) |
| 500 mg iron | 22 | 8 (36%) |

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**

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

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, ie, 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.

Danielson BG. Oral and intravenous iron supplementation in renal anemic patients on EPO treatment. Internal report. 1993a; Danielson BG. Supplementation with IV iron sucrose complex in patients with anemia. Internal report. 1993b.

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 one 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).**

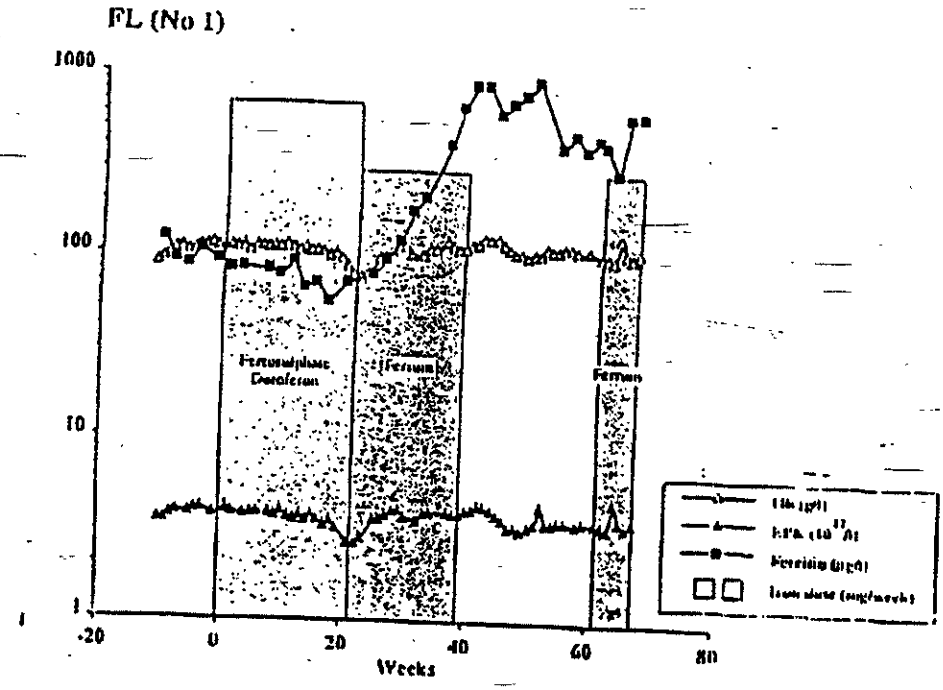


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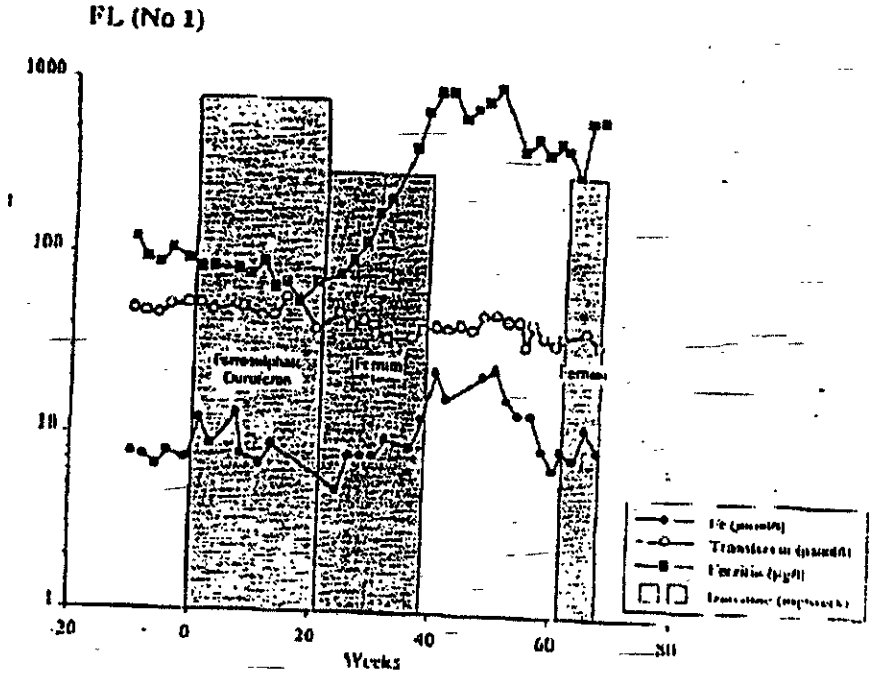
**Figure 9** **For Patient No. 1, Time Course of Iron (Fe), Transferrin, and Ferritin During Treatment With Ferrosulphate Duroferon® (Oral Iron) and IV Iron Sucrose (Ferrum [Hausmann®] IV, Ferrum).**




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

Al-Momem AK et al. Intravenous iron saccharate in hemodialysis patients receiving r-HuEPO. *Saudi J Kidney Dis Transplant*. 1994; 5(2): 168-172.

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**

| Test | Group 1 - "High Dose" - 500 Mg Iron (N=58) | | | | Group 2 – "Low Dose" - 100 Mg Iron (N=51) | | | |
|---|---|---|---|---|---|---|---|---|
| | Iron Deficient (n=42) | | Non-Iron Deficient (n=16) | | Iron Deficient (n=22) | | Non-Iron Deficient (n=29) | |
| | A† | B | A | B | A | B | A | B |
| Hb (g/dL) | 8.3±0.7 | 11.0*±0.7 | 8.8±0.6 | 11.6*±0.6 | 8.5±0.3 | 11.1*±1.0 | 8.5±0.8 | 11.2*±1.0 |
| Hct (%) | 24.9±2.3 | 33.0*±2.1 | 26.5±2.1 | 35.0*±1.9 | 25.7±1.8 | 33.4*±2.8 | 25.4±2.6 | 34.1*±2.9 |
| MCV (fL) | 71.7±4.7 | 81.4*±3.5 | 83.7±4.2 | 83.7±3.0 | 68.2±4.5 | 75.4*±4.4 | 84.7±4.2 | 85.2±3.8 |
| MCH (pg) | 24.5±2.7 | 30.9*±1.5 | 31.4±0.9 | 31.1±0.8 | 22.1±2.5 | 28.4*±1.5 | 32.1±1.2 | 31.9±1.1 |
| Fe(µmol/L) | 11.0±2.9 | 18.7*±4.6 | 19.8±2.9 | 21.6±2.8 | 7.2±3.2 | 15.2*±2.4 | 19.9±3.8 | 21.1±3.4 |
| TIBC (µmol/L) | 80.4±5.3 | 57.9*±9.8 | 50.8±5.7 | 48.7±5.6 | 97.7±6.4 | 55.5*±9.4 | 55.5±8.1 | 47.6±6.0 |
| Ferritin (ng/mL) | 18.6±11.8 | 52.2*±25.3 | 165.0±46.3 | 200.0±38.3 | 12.8±6.0 | 88.7*±23.0 | 107.5±38.5 | 177.5±66.5 |

†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
g/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

Silverberg DS et al. Intravenous iron supplementation for the treatment of the anemia of moderate to severe chronic renal failure patients not receiving dialysis. *Amer J Kidney Diseases.* 1996; 27(2): 234-238.

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 twice 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**

| | Time of Measure | | |
|---|---|---|---|
| | Initial‡ | +3 Months | +6 Months |
| Parameter† | | | |
| Hematocrit (%) | 29.6±2.8 | 31.4±2.6 | 31.5±3.1 * |
| Hemoglobin (g/dL) | 10.0±1.1 | 10.5±0.9 | 10.6±1.1 * |
| Serum Iron (µg/dL) | 76.1±5.1 | 78.1±4.9 | 85.1±5.1 * |
| TIBC (µg/dL) | 343.7±60.0 | 306.4±41.8 * | 311.6±40.7 * |
| Iron Saturation (%) | 22.1±7.1 | 25.5±8.1 * | 27.3±8.2 * |
| Serum Ferritin (µg/L) | 106±95 | 190.4±108.0 * | 297±192 * |

† Data are presented at means±standard deviations.
‡ Values determined immediately before onset of treatment.
* P<0.05 by two-tailed Student's paired *t*-test, at least compared to initial values.
g/dL: gram per deciliter, µg/dL: microgram per deciliter, L: liter.

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 JJM. In vitro binding of iron saccharate to human tranferrin. Communication
Geisser P. Comments on the publication from C.E. van Iperen et al. "In vitro binding of iron saccharate to human transferrrin". 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 osmolarity of 1250 mosm/L and a pH of 10.5-11.1. No preservatives are added and for pH adjustment a solution of [redacted] 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 [$(Fe_5O_8H{\cdot}4(H_2O))$] 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 $[Na_pFe_5O_8(OH)_r{\cdot}x(H_2O)]_L{\cdot}m(C_{12}H_{22}O_{11})$ where: $p = 2.30$; $r = 1.3$; $x = 2.70$; $L = 8.60$; $m = 112.23$.

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

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## Attachment C DRUG FORMULATION DEVELOPMENT SUMMARY

**Luitpold Pharmaceuticals, Inc.**
**Venofer®**
**IND#: —**
**NDA#: 21-135**

| Study Number | Lot. No. | Dosage Form and Strength[a] | Batch Size/ Manufacturer & Site | Formulation or Significant Manufacturing Change (if any) and Reason for Change | Effect of Change |
|---|---|---|---|---|---|
| **Clinical Studies** | | | | | |
| Bernière J. et al (Report. 12.3.1998) | 535109 A1 | Venofer® IV<br>100 mg iron/5 mL ampule | | Not applicable | |
| Beshara S. et al (Internal Report. 14.5.1997) | 671109 | Venofer® IV<br>100 mg iron/ 5 mL ampule | | — Due to change in manufacturing site from — where ampules were no longer manufactured, to — | None |
| Chandler G. et al (Internal Report. VIF95002, 1998) | 572109<br>670109<br>675109 | Venofer® IV<br>100 mg iron/ 5 mL ampule | | — Due to change in manufacturing site from — where ampules were no longer manufactured, to — | None |
| Danielson B.G. et al (Internal Report. 7.7.1995) | 445209-B1 | VenoFerrum<br>100 mg iron/5 mL ampule | | Not applicable | |
| Hussain et al, 1999 | 558109 A2 | VenoFerrum<br>100 mg iron/5 mL ampule | | Not applicable | |
| Macdougall I.C. et al (Internal Report. March 5, 1999) | 535109 A1<br>692109 A1<br>554209 A2 | Venofer® IV<br>100 mg iron/5mL ampule | | Not applicable | |
| Meyer M.P. et al, (publication) 1996 | 447209 A1 | VenoFerrum<br>100 mg iron/5 mL ampule | | Not applicable | |
| DePree et al, 1997<br>Beris et al, 1999 | 293209 | Ferrum IV<br>100 mg iron/5 mL ampule | | Not applicable | |

a: Ferrum IV, VenoFerrum and Venofer IV are identical products.

## Attachment C DRUG FORMULATION DEVELOPMENT SUMMARY (continued)

| Study Number | Lot. No. | Dosage Form and Strength[a] | Batch Size/ Manufacturer & Site | Formulation or Significant Manufacturing Change (if any) and Reason for Change | Effect of Change |
|---|---|---|---|---|---|
| Al-Momen et al, 1999 | Not known | Not known | | Not applicable | |
| Schaefer R.M. et al, (Study Report.1999) | 670109 | Venofer® IV<br>100 mg iron/5 mL ampule | | [redacted] Due to change in manufacturing site from [redacted] where ampules were no longer manufactured, to [redacted] | None |
| Van Zyl-Smit R et al (Study Report. VENO/BGSA-VIFOR/001 FARMOVS 52/93, May 26, 1997 | 447209 A1 | VenoFerrum<br>100 mg iron in 5 mL ampule | | Not applicable | |
| LU98001 | RD98005<br><br>RD98012 | Venofer® IV<br>100 mg iron/5 mL vial<br>Venofer® IV<br>100 mg iron/5 mL vial | | Filling of vials under [redacted] rubber stoppers used. | None |
| LU98002 | RD98012 | Venofer® IV<br>100 mg iron/5 mL vial | | Filling of vials under [redacted] rubber stoppers used. | None |
| **Preclinical Studies** | | | | | |
| Arzneim-Forsch./Drug 1992 | 750208 | Ferrum IV<br>100 mg iron in 5 mL ampule | | Not applicable | |
| VFR 1/5_1736<br>January 15, 1995 | 330109 A2 | Ferrum IV<br>100 mg iron in 5 mL ampule | | Not applicable | |
| VFR 2/951737<br>January 15, 1995 | 330109 A2 | Ferrum IV<br>100 mg iron in 5 mL ampule | | Not applicable | |
| VFR 4/950317<br>June 7, 1995 | 330109 A2 | Ferrum IV<br>100 mg iron in 5 mL ampule | | Not applicable | |
| VFR 3/951491<br>December 20, 1995 | 330109 A2 | Ferrum IV<br>100 mg iron in 5 mL ampule | | Not applicable | |

a: Ferrum IV, VenoFerrum and Venofer IV are identical products.

## Attachment C DRUG FORMULATION DEVELOPMENT SUMMARY (continued)

| Study Number | Lot. No. | Dosage Form and Strength[a] | Batch Size/ Manufacturer & Site | Formulation or Significant Manufacturing Change (if any) and Reason for Change | Effect of Change |
|---|---|---|---|---|---|
| VFR 5/951735<br>December 21, 1995 | 330109 A2 | Ferrum IV<br>100 mg iron in 5 mL ampule | | Not applicable | |
| VFR 012/1211<br>January 10, 1997 | 572109 | Venofer® IV<br>100 mg iron in 5 mL ampule | | Due to change in manufacturing site from — where ampules were no longer manufactured, to — | None |
| VFR 014/971264<br>April 29, 1997 | 572109 | Venofer® IV<br>100 mg iron in 5 mL ampule | | Due to change in manufacturing site from — where ampules were no longer manufactured, to — | None |
| VFR 15/972400<br>September 18, 1997 | 676109 | Venofer® IV<br>100 mg iron in 5 mL ampule | | Due to change in manufacturing site from —, where ampules were no longer manufactured, to — | None |
| VFR 16/974254<br>December 29, 1997 | 676109 | Venofer® IV<br>100 mg iron in 5 mL ampule | | Due to change in manufacturing site from — where ampules were no longer manufactured, to — | None |
| SR-1020/E01<br>December 9, 1997 | 572109 | Venofer® IV<br>100 mg iron in 5 mL ampule | | Due to change in manufacturing site from — where ampules were no longer manufactured, to — | None |

a: Ferrum IV, VenoFerrum and Venofer IV are identical products.

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## 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.

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# Attachment D IN VIVO ANALYTICAL METHODS SUMMARY

**Luitpold Pharmaceuticals, Inc. Venofer®**
**IND #:**
**NDA #: 21-135**

| Paren Drug: Iron sucrose<br>Study/Test | Submission Date | Type of Biol. Fluid | Method | Sensitivity of Method/Range | Specificity (parent/metabolites) |
|---|---|---|---|---|---|
| Macdougall et al, March 5, 1999<br>1. Iron<br>2. Total circulating iron<br>3. Hemoglobin<br>4. Serum ferritin | | Serum | | Not reported | Not reported |
| Danielson et al, 1995<br>1. Elemental iron<br>2. Sucrose<br>3. Transferrin receptor<br>4. Total iron binding capacity | October 15, 1998 | 1. Serum and urine<br>2. Urine<br>3. Serum<br>4. Serum | | 1. Sensitivity: 10-1000µmol/L; relative standard deviation of method: 5.6% (n=63, x=25.8µmol/L, SD: 44µmol/L<br>2. Not reported<br>3. Normal range: 1.54 ± 0.43 mg/L (95% confidence intervals: 0.85-3.05 mg/L)<br>4. Not reported | Iron (no metabolites) |
| Beshara et al, 1997<br>1. $^{52}Fe/^{59}Fe$<br>2. Iron status: Serum iron, total iron binding capacity, transferrin saturation, serum ferritin<br>3. Serum transferrin receptor | October 15, 1998 | 1. Whole blood, plasma, packed red cells, liver, left ventricle of heart, bone marrow, spleen<br>2. Serum<br>3. Serum | | 1. Not reported<br>2. Not reported<br>3. Normal range: 1.54 ± 0.43 mg/L (95% confidence intervals: 0.85-3.05 mg/L) | 1. $^{52}Fe$ and $^{59}Fe$ (and metabolite $^{52}Mn$)<br>2. Serum iron, total iron binding capacity, transferrin saturation, ferritin (no metabolites)<br>3. Serum transferrin receptor |

WHO=World Health Organization; Fe=iron; Mn=manganese; Ga=gallium; Ge=germanium

## Attachment D In Vivo Analytical Methods Summary (continued)

**Luitpold Pharmaceuticals, Inc. Venofer®**
**IND #:**
**NDA #: 21-135**

| Parent Drug: Iron sucrose Study/Test | Submission Date | Type of Biological Fluid | Method | Sensitivity of Method/Range | Specificity (parent/ metabolites) |
|---|---|---|---|---|---|
| Krzysko K, Bokowski W, and Wichlinski, LM. 1984 Iron | October 15, 1998 | Serum | | Not reported | Iron (no metabolites) |
| Anatkov and Gekova, 1970<br>1. Iron<br>2. Total iron binding capacity | October 15, 1998 | 1.a. Serum<br>1.b. Urine<br>2. Serum | | Not reported | Iron and total iron binding capacity |
| Major et al, 1997<br>1. Hemoglobin<br>2. EPO content<br>3. Serum ferritin | October 15, 1998 | Blood red cells, reticulocytes; serum | | Not reported | Not reported |
| Chandler G, Harchowal J and Macdougall K, VIF95002, 1998 Side effects evaluated | October 15, 1998 | Not applicable | | Not applicable | Not applicable |
| Danielson 1993a, 1993b<br>1. Hematological indices<br>2. Serum chemistry tests<br>3. Intact PTH<br>4. Aluminum | October 15, 1998 | 1. Blood<br>2. Serum<br>3. Serum<br>4. Serum | | 1. Not reported<br>2. Reference values for serum phosphate and serum alkaline phosphatase: 0.76-1.44 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).<br>3. Reference range: 10-55 ng/L<br>4. Normal value <10 µg/L. | Not reported |

EPO=erythropoietin



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## Attachment D In Vivo Analytical Methods Summary (continued)

**Luitpold Pharmaceuticals, Inc. Venofer®**
**IND #: ——**
**NDA #: 21-135**

| Parent Drug: Iron sucrose Study/Test | Submission Date | Type of Biological Fluid | Method | Sensitivity of Method/Range | Specificity (parent/ metabolites) |
|---|---|---|---|---|---|
| Al-Momen et al, 1994.<br>1. Hematological parameters<br>2. Serum iron, iron binding capacity<br>3. Ferritin | October 15, 1998 | 1. Blood<br>2. Serum<br>3. Serum | | Not reported | Not reported |
| Silverberg et al, 1996.<br>Complete blood count, creatinine, ferritin, total iron binding capacity,<br>creatinine clearance, iron saturation | October 15, 1998 | Blood, serum | | Not reported | Not reported |

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# PROPOSED PACKAGE INSERT



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 Arabai
17. South Korea
18. Sri Lanka
19. Thailand
20. Tunisia
21. Turkey
22. Uruguay

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# 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 complex-formation with the protein ligand apoferritin of the mitochondria of the liver.
Iron is transported in the blood plasma bound to a β-globulin, transferrin. This protein reacts with two atoms of iron per protein molecule, with the formation of a pink-coloured complex. The major function of transferrin is to act as the carrier of iron through the body (transportation to the sites of haemoglobin- and myoglobin-synthesis 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 level 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 administration.

**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 haemorrhages,
- disturbances in iron absorption in the gastro-intestinal tract,
- marked incompatibility of oral iron preparations,
- iron deficiency resistant to treatment, when the patient cannot be relied on to take the tablets, and
- contact 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 average, administration of 100 mg Fe(III) (= 1 ampoule of 5 ml) results in an increase 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 total dosage of iron has been calculated from the following formula:

# Venofer®

## intraveineux

**Composition**
Solution aqueuse alcaline standardisée d'un complexe d'hydroxyde ferrique et de sucrose. Une ampoule de 5 ml contient 100 mg de fer trivalent.

**Mode d'action**
L'hydroxyde ferrique polynucléaire est en partie emmagasiné sous forme de ferritine (fer de réserve) après formation d'un complexe avec le colloïde protéinique des mitochondries du foie, l'apoferritine.
Dans le plasma sanguin, le fer est transporté lié à une β-globuline: la transferrine. Cette protéine est capable de fixer deux atomes de fer par molécule, avec formation d'un complexe de couleur rose. La transferrine a pour fonction essentielle de véhiculer le fer dans l'organisme (transport vers les lieux de synthèse de l'hémoglobine 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 participation aux mécanismes de défense du corps contre les infections.
Après emploi du Venofer I.V., le taux d'hémoglobine s'élève plus rapidement et plus sûrement qu'après traitement aux sels ferreux par voie orale, bien que les processus cinétiques de résorption du fer soient indépendants de son mode d'administration.

**Indication**
Tous les cas de carence martiale où une administration de fer rapide et sûre s'avère nécessaire:
- spécialement lors d'états de carence grave, après hémorragie par exemple,
- lors de troubles d'absorption dans le tractus gastrointestinal,
- lors d'intolérances nettes à l'administration orale de fer,
- lors d'un état de carence martiale résistant au traitement per os, au cours duquel l'observance du malade peut être mise en doute,
- lorsque les consultations médicales sont trop espacées et irrégulières.

**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'hémoglobine.

**Posologie**
En moyenne, l'administration de 100 mg de Fe(III) (soit 1 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 maximale 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 normal d'hémoglobine: 15 g/100 ml pour un volume de sang correspondant à 7% du poids total du corps; taux de fer dans l'hémoglobine: 0,34%; nécessité d'une quantité de fer de réserve égale à 500 mg*.

**Dose totale de fer en mg**
(voir aussi tableau)
Le calcul a été effectué en utilisant la formule suivante:

# Venofer®

## intravenoso

**Composición**
Solución acuosa alcalina del complejo hidróxido férrico con sucrosa estandarizada. Una ampolla de 5 cc. contiene 100 mg de hierro trivalente.

**Modo de acción**
El hidróxido férrico polinuclear, después de haber formado el complejo con la apoferritina (ligador proteico de las mitocondrias del hígado), se almacena en parte bajo la forma de ferritina (hierro retard).
En el plasma a de la sangre, el hiero se transporta ligado con la transferrina, una β-globulina. Esta proteína reacciona con dos atomos de hierro por molécula de proteina, formándose un complejo de color rosado. La transferrina tiene por función principal el transporte del hierro a través del cuerpo (llevándolo a los lugares de síntesis de la hemoglobina y de la mioglobina, así como hacia las células productoras de fermentos que contienen hierro).
La transferrina, por lo tanto, desempeña un papel de vital importancia dentro del metabolismo del hierro; además posee otra función muy importante, la de tomar parte en el mecanismo de defensa del organismo contra las infecciones.
Con la terapia endovenosa, el nivel de hemoglobina aumenta de forma mas rapida y segura que con terapia por via bucal con sáles ferrosas, a pesar de que los procesos cinéticos de incorporación de hierro no dependan del modo de administración.

**Indicaciones**
En todos los casos de deficiencia de hierro, en los cuales una sustitución rápida y segura es necesaria:
- En particular, en casos graves de deficiencia 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 administración oral de preparados de hierro.
- En casos de deficiencia de hierro refractarios al tratamiento, en los cuales el médico no puede fiarse en la disciplina del enfermo.
- En casos de contactos demasiado irregulares entre enfermo y médico.

**Dosificación**
El primar día: 2,5 cc. = 50 mg. de Fe(III)
El segundo día: 5,0 cc. = 100 mg. de Fe(III)
El tercer día: 10,0 cc. = 200 mg. de Fe(III)
Continuar administrando dos veces por semana 10 cc. cada vez, según el nivel de hemoglobina existente (según critero facultativo).

**Posologia**
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 utilizándose el método o el cuadro de más abajo.
La dosis necesaria puede determinarse a base de un nivel de hemoglobina normal de 15 grs./100 cc. para un volumen de sangre, estimado a un 7% del peso del cuerpo, un porcentaje de hierro en la hemoglobina de 0,34% y la necesidad de una cantidad de hierro retard de 500 mg*.

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

**Total iron deficiency in mg = Hb-iron deficiency + depot iron**

**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-Fe deficit:

| | |
|---|---|
| 70 x (150–80) 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 (¼ ampoule) |
| Children between 5–10 kg | 2.5 ml (½ 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. Therefore 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 Venofer® with any other medicament.

**Contra-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.

* K. Rhyner and A. M. Ganzoni, Schweiz. med. Wschr. 102, 561–565 (1972).

**Déficit en fer total en mg = déficit en fer (Hb) + réserves de fer**

**Déficit en fer (Hb) en mg = poids corporel (kg) x (Hb normale – Hb actuelle en g/l) x 0,24***

Ce calcul est basé sur:
- la valeur d'hémoglobine normale: 150 g/l pour un poids corporel de plus de 35 kg, 130 g/l jusqu'à 34 kg
- la teneur en fer de l'hémoglobine (0,34%)
- le volume de sang (env. 7% du poids corporel) et
- les besoins en fer de réserve (env. 15 mg par kg pour un poids jusqu'à 34 kg env., besoin total de 500 mg pour un poids de plus de 34 kg).

* Facteur 0,24 = 0,0034 x 0,07 x 1000

**Exemple**
Patient pesant 70 kg
Hb normale: 150 g/l
Hb actuelle: 80 g/l
Déficit en Fe (Hb):

| | |
|---|---|
| 70 x (150–80) x 0,24 = | 1176 mg de fer |
| Besoin en fer de réserve | 500 mg de fer |
| Dose totale | 1676 mg de fer |

Par conséquent, ce patient a besoin de 1700 mg de fer, soit 17 ampoules pendant le traitement.

**Doses maximales journalières**

| | |
|---|---|
| Enfants jusqu'à 5 kg | 1,25 ml (¼ ampoule) |
| Enfants de 5 à 10 kg | 2,5 ml (½ ampoule) |
| Adultes | 10,0 ml (2 ampoules) |

**Effets secondaires**
Dans de très rares cas des reactions anaphylactoïdes ont été observées. Les mesures à prendre dans ces cas sont les mêmes que pour toute anaphylaxie.

**Précautions**
En cas de stockage dans de mauvaises conditions, on peut observer la formation de sédiments dans les ampoules. Il convient donc de bien examiner les ampoules, et en particulier le haut et le bas de celles-ci, avant toute injection. Ne pas utiliser le contenu d'ampoules présentant une sédimentation ou ayant dépassé la date limite de conservation.
Stockage entre 4 et 25° C.
Ne mélanger le Venofer® avec aucun autre médicament.

**Contre-indications**
Tous les cas de surcharge en fer ou de troubles de l'utilisation du fer.

**Formes commerciales**
5, 50 et 100 ampoules de 5 ml/100 mg de fer chacune.

* K. Rhyner et A. M. Ganzoni, Schweiz. med. Wschr. 102, 561–565 (1972).

**Deficiencia total de hierro en mg = Deficiencia de hierro Hb + hierro de reserva**

**Deficiencia de hierro Hb (en mg) = Peso del cuerpo (kg) x (Hb normal – actual en g/l) x 0,24***

Este cálculo se basa en:
- un Hb normal de 150 g/l para pesos del cuerpo mayores de 35 kg respectivamente 130 g/l hasta 34 kg de peso del cuerpo
- el contenido de hierro de hemoglobina (0,34%)
- el volumen de sangre (aprox. 7% del peso del cuerpo) y
- las necesidades de hierro de reserva (aprox. 15 mg por kg hasta un peso de unos 34 kg, un total de 500 mg por encima de 34 kg).

* Factor 0,24 = 0,0034 x 0,07 x 1000

**Ejemplo**
Peso del paciente 70 kg
Hb normal: 150 g/l
Hb actual: 80 g/l
Deficiencia de Fe-Hb:

| | |
|---|---|
| 70 x (150–80) x 0,24 = | 1176 mg de Fe |
| Necesidad de hierro de res. | 500 mg de Fe |
| Dose total | 1676 mg de Fe |

Por consiguiente este paciente necesita 1700 mg de hierro ó 17 ampollas durante el tratamiento.

**Dosis máxima diaria**

| | |
|---|---|
| Niños hasta 5 kg de peso corporal | 1,25 ml (¼ ampolla) |
| Niños de 5–10 kg de peso corporal | 2,5 ml (½ ampolla) |
| Adultos | 10,0 ml (2 ampollas) |

**Efectos secundarios**
Raramente se producen reacciones anafiláctoideas. En estos casos, las medidas a tomar, son las mismas que para cualquier otra anafilaxia.

**Precauciones**
En caso de almacenaje inconveniente, no se puede excluir la formación de sedimentos. Por tal motivo, las ampollas deben examinarse con esmero antes de inyectarlas, particularmente su parte superior e inferior.
No aplicar el contenido de tales ampollas que presentan sedimentación o la fecha de las cuales ha expirado ya.
Temperatura de almacenaje recomendada 4 – 25° C.
No mezclar Venofer® con cualquier otro medicamento.

**Contraindicaciones**
Todos los casos de sobrecarga con hierro o de trastornos en la utilización del hierro.

**Formas comerciales**
5, 50 y 100 ampollas de 5 cc./100 mg de hierro cada una.

* K. Rhyner y A. M. Ganzoni, Schweiz. med. Wschr. 102, 561–565 (1972).

| | Body weights / Poids du corps / Peso corporal | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 5 kg | 10 kg | 15 kg | 20 kg | 25 kg | 30 kg | 35 kg | 40 kg | 45 kg | 50 kg | 55 kg | 60 kg | 65 kg | 70 kg | 75 kg | 80 kg | 85 kg | 90 kg |
| Hb = 60 g/l | Amp. 1,5 | 3 | 5 | 6,5 | 8 | 9,5 | 12,5 | 13,5 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22,5 | 23,5 | 24,5 |
| Hb = 75 g/l | Amp. 1,5 | 3 | 4,5 | 5,5 | 7 | 8,5 | 11,5 | 12 | 13 | 14 | 15 | 16 | 16,5 | 17,5 | 18,5 | 19,5 | 20,5 | 21,5 |
| Hb = 90 g/l | Amp. 1,5 | 2,5 | 3,5 | 5 | 6 | 7,5 | 10 | 11 | 11,5 | 12 | 13 | 13,5 | 14,5 | 15 | 16 | 16,5 | 17 | 18 |
| Hb = 105 g/l | Amp. 1 | 2 | 3 | 4 | 5,5 | 6,5 | 9 | 9,5 | 10 | 10,5 | 11 | 11,5 | 12 | 12,5 | 13 | 13,5 | 14 | 14,5 |

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# VENOFER® PACKAGE INSERT FOR:

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# Venofer®

## Intravenous iron therapy

**QUALITATIVE AND QUANTITATIVE COMPOSITION**
1 ml containing:
Iron as iron(III)-Hydroxide Sucrose Complex 20 mg

**PHARMACEUTICAL FORM**
Solution for injection.

**CLINICAL PARTICULARS**
**Therapeutic indications**
Venofer® is indicated for parenteral treatment of iron deficiency in cases whereby oral iron preparations cannot provide for sufficient supplementation such as:
- patients who cannot tolerate oral iron therapy
- patients who cannot sufficiently absorb orally administered iron

**Posology and method of administration**
*Administration*
Venofer® has exclusively to be administered intravenously by drip infusion, by slow injection or directly into the venous limb of the dialyser and is not suitable for intramuscular use and for total dose infusion (TDI), where the full dose of iron required, representing the patients total iron deficit is administered in one complete infusion.
Before administration of the first therapeutic dose of Venofer® in a new patient, a test dose of 1 to 2.5 ml Venofer® (20 to 50 mg iron) in adults, 1 ml (20 mg iron) in children >14 kg and half the daily dose (1.5 mg/kg) in children <14 kg should be given by the chosen method of administration. Facilities for cardio-pulmonary resuscitation must be available. If no adverse reactions occur within a waiting period of at least 15 minutes after administration the remaining portion of the initial dose can be given.

*Infusion:* Venofer® may preferably be administered by drip infusion (in order to reduce the risk of hypotensive episodes and paravenous injection). 1 ml Venofer® (20 mg iron) has to be diluted exclusively in max. 20 ml of 0.9% sodium chloride solution, immediately prior to infusion (i.e. 5 ml in max. 100 ml 0.9% NaCl up to 25 ml in max. 500 ml 0.9% NaCl). The solution should be infused at a rate of: 100 ml in at least 15 minutes; 200 ml in at least 30 minutes; 300 ml in at least 1.5 hours; 400 ml in at least 2.5 hours; 500 ml in at least 3.5 hours.
*Intravenous injection:* Venofer® may be administered by slow intravenous injection at a rate of 1 ml undiluted solution per minute (i.e. 5 minutes per 5 ml ampoule) not exceeding 10 ml Venofer® (200 mg iron) per injection. After an injection, extend the arm of the patient.
*Injection into dialyser:* Venofer® may be administered directly into the venous line of the dialyser under the same conditions as for intravenous injection.

**Dosage**
*Calculation of dosage:*
The dosage has to be individually adapted according to the total iron deficit calculated with the following formula:
Total iron deficit [mg] = body weight [kg] x (target Hb – actual Hb) [g/l] x 0.24* + depot iron [mg]
Up to 35 kg body weight: target Hb = 130 g/l resp. depot iron = 15 mg/kg body weight
Above 35 kg body weight: target Hb = 150 g/l resp. depot iron = 500 mg

* Factor 0.24 = 0.0034 x 0.07 x 1000
(Iron content of haemoglobin = 0.34%/Blood volume = 7% of body weight/Factor 1000 = conversion from g to mg)

Total amount of Venofer® to be administered [in ml] =

$$\frac{\text{Total iron deficit [mg]}}{\text{20 mg/ml}}$$

# Venofer®

## Thérapie martiale intraveineuse

**COMPOSITION QUALITATIVE ET QUANTITATIVE**
1 ml contient:
du fer sous forme de complexe d'hydroxyde de fer(III)-saccharose 20 mg

**FORME PHARMACEUTIQUE**
Solution injectable.

**DONNÉES CLINIQUES**
**Indications thérapeutiques**
Venofer® est indiqué dans le traitement parentéral des déficits en fer, dans les cas où les préparations martiales per os ne suffisent pas à assurer une supplémentation adéquate tels que:
- chez les patients ne tolérant pas le traitement martial per os
- chez les patients qui ne peuvent absorber suffisamment le traitement martial per os

**Posologie et mode d'administration**
*Administration*
Venofer® doit être administré par voie intraveineuse stricte en perfusion, en injection lente ou directement dans le circuit sanguin extracorporel en hémodialyse. Venofer® ne doit pas être utilisé par voie intramusculaire et sous forme de perfusion de la dose totale (quand la totalité de la dose nécessaire, représentant le déficit en fer total est administrée en une perfusion unique).
Avant administration de la première dose thérapeutique de Venofer®, chez un nouveau patient, une dose test de 1 à 2,5 ml de Venofer® (20 à 50 mg de fer) chez l'adulte, de 1 ml (20 mg de fer) chez l'enfant de plus de 14 kg et de la moitié de la dose journalière (1,5 mg/kg) chez l'enfant de moins de 14 kg, doit être réalisée en utilisant la méthode d'administration choisie. Des moyens de réanimation doivent être à disposition. Si aucun effet indésirable n'est observé pendant une période d'attente d'au moins 15 minutes suivant cette injection, le reste de la dose initiale peut être injecté à vitesse normale.
*Perfusion:* il est préférable d'administrer Venofer® en perfusion pour diminuer les risques d'hypotension et d'injection périveineuse. Venofer® doit être dilué exclusivement dans du NaCl 0,9%, à raison de 1 ml (20 mg de fer) dans 20 ml max. de NaCl 0,9%, immédiatement avant la perfusion (c. à. d. 5 ml dans 100 ml max. de NaCl 0,9% jusqu'à 25 ml [500 mg de fer] dans 500 ml max. de NaCl 0,9%). La solution obtenue doit être perfusée à raison de 100 ml en 15 minutes au moins; 200 ml en 30 minutes au moins; 300 ml en 1 h. 30 au moins; 400 ml en 2 h. 30 au moins et 500 ml en 3 h. 30 au moins.
*Injection intraveineuse:* Venofer® peut être administré par voie intraveineuse lente à raison de 1 ml de solution non diluée par minute (soit 5 minutes par ampoule de 5 ml) sans dépasser 10 ml de Venofer® (200 mg de fer) par injection. Après l'injection, étendre le bras du patient.
*Injection dans un dialyseur:* Venofer® peut être administré directement dans le pôle veineux du circuit sanguin extracorporel du dialyseur dans les mêmes conditions que pour une injection intraveineuse.

**Posologie**
*Calcul des posologies:*
La posologie doit être adaptée individuellement en tenant compte du déficit en fer total, calculé selon la formule suivante:
Déficit en fer total [mg] = poids corporel [kg] x (Hb cible – Hb actuelle) [g/l] x 0,24* + réserves de fer [mg]
Jusqu'à 35 kg: Hb cible = 130 g/l et réserves de fer = 15 mg/kg de poids corporel
Au-dessus de 35 kg: Hb cible = 150 g/l et réserves de fer = 500 mg

* facteur 0,24 = 0,0034 x 0,07 x 1000 (contenu de l'hémoglobine en fer = 0,34%, volume sanguin = 7% du poids corporel, facteur 1000 = conversion des g en mg).

Quantité totale de Venofer® à administrer (en ml) =

$$\frac{\text{Déficit en fer total (mg)}}{\text{20 mg/ml}}$$

# Venofer®

## Tratamiento férrico intravenoso

**COMPOSICIÓN CUALITATIVA Y CUANTITATIVA**
1 ml contiene:
Hierro en forma de complejo de sacarosa e hidróxido férrico 20 mg

**FORMA FARMACÉUTICA**
Solución inyectable

**PARTICULARES CLÍNICOS**
**Indicaciones terapéuticas**
Venofer® es indicado para el tratamiento parenteral de deficiencia de hierro en casos en que preparaciones orales no pueden providenciar el suplemento suficiente como:
- pacientes que no toleran el tratamiento oral de hierro
- pacientes que no pueden absorber suficientemente el hierro administrado por vía oral

**Posología y método de administración**
*Administración*
Venofer® debe administrarse únicamente por vía intravenosa mediante infusión; inyección lenta o directamente en la parte venosa del aparato de diálisis y no es adecuado para el uso intramuscular y la infusión como dosis total (TDI) en casos en cuales es necesario que la dosis completa de hierro sea administrada en una infusión completa, representando el deficit de hierro total del paciente.
Antes de la administración de la primera dosis terapéutica de Venofer® en un nuevo paciente, se debe aplicar una dosis de prueba por el método de administración elegido de 1 a 2,5 ml de Venofer® (20 a 50 mg de hierro) en adultos, 1 ml (20 mg de hierro) en niños con mas de 14 kg y la mitad de la dosis diaria (1,5 mg/kg) en niños con menos de 14 kg. Deben estar disponibles instalaciones para la resucitación cardiopulmonar. Si en un periodo de espera de 15 min. como mínimo posterior a la administración no aparecen reacciones adversas, se puede administrar la cantidad restante de la dosis inicial.
*Infusión:* Venofer® debe administrarse preferentemente por infusión (para reducir el riesgo de episodios hipotensivos y de inyección paravenosa). 1 ml de Venofer® (20 mg de hierro) tiene que ser diluido exclusivamente en max. 20 ml de solución de cloruro sódico al 0,9% inmediatamente antes de la infusión (i.e. 5 ml en max. 100 ml de NaCl al 0,9% hasta 25 ml en max. 500 ml de NaCl al 0,9%). La solución tiene que ser infundida con una velocidad de: 100 ml en 15 min. como mínimo; 200 ml en 30 min. como mínimo; 300 ml en 1,5 h. como mínimo; 400 ml en 2,5 h. como mínimo; 500 ml en 3,5 h. como mínimo.
*Inyección intravenosa:* Venofer® puede administrarse por inyección lenta intravenosa con una velocidad de 1 ml de solución no diluida por minuto (i.e. 5 minutos por ampolla de 5 ml) sin sobrepasar 10 ml de Venofer® (200 mg de hierro) por inyección. El brazo del paciente debe extenderse después de una inyección.
*Inyección en el aparato de diálisis:* Venofer® puede administrarse directamente en la parte venosa del aparato de diálisis bajo las mismas condiciones de la inyección intravenosa.

**Dosificación**
*Cálculo de la dosificación:*
La dosificación debe adaptarse individualmente según el déficit de hierro total, que se calcula con la fórmula siguiente:
Déficit de hierro total [mg] = Peso corporal [kg] x (Hb teórica – Hb real) [g/l] x 0,24* + Hierro de reserva [mg]
Hasta 35 kg peso corporal: Hb teórica = 130 g/l; hierro de reserva = 15 mg/kg peso corporal
A partir de 35 kg peso corporal: Hb teórica = 150 g/l; hierro de reserva = 500 mg

* factor 0,24 = 0,0034 x 0,07 x 1000 (contenido de hierro de la hemoglobina = 0,34%/volumen sanguíneo = 7% del peso corporal/factor 1000 = conversión de g en mg)

Cantidad total a ser administrada de Venofer® =

$$\frac{\text{déficit total de hierro [mg]}}{\text{20 mg/ml}}$$

| | Body weight/Poids corporel/Peso corporal | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 5 kg | 10 kg | 15 kg | 20 kg | 25 kg | 30 kg | 35 kg | 40 kg | 45 kg | 50 kg | 55 kg | 60 kg | 65 kg | 70 kg | 75 kg | 80 kg | 85 kg | 90 kg |
| Hb = 60 g/l | 8 | 16 | 24 | 32 | 40 | 48 | 53 | 68 | 74 | 79 | 84 | 90 | 95 | 101 | 106 | 111 | 117 | 122 |
| Hb = 75 g/l | 7 | 14 | 21 | 28 | 35 | 42 | 57 | 61 | 66 | 70 | 75 | 79 | 84 | 88 | 93 | 97 | 102 | 106 |
| Hb = 90 g/l | 6 | 12 | 19 | 25 | 31 | 37 | 50 | 54 | 57 | 61 | 65 | 68 | 72 | 75 | 79 | 83 | 86 | 90 |
| Hb = 105 g/l | 5 | 11 | 16 | 21 | 26 | 32 | 44 | 47 | 49 | 52 | 55 | 57 | 60 | 63 | 66 | 68 | 71 | 74 |

If the total necessary dose exceeds the maximum allowed single dose, then the administration has to be split. If no response of the haematological parameters is observed after 1 to 2 weeks the original diagnosis should be reconsidered.

**Calculation of dosage for iron replacement secondary to blood loss and to support autologous blood donation**
The required Venofer® dose to compensate the iron deficit is calculated according the following formulas:
- *If the quantity of blood lost is known:* The administration of 200 mg i.v. iron (= 10 ml Venofer®) results in an increase in haemoglobin which is equivalent to 1 unit blood (= 400 ml with 150 g/l Hb content).
  Iron to be replaced [mg] = number of blood units lost x 200
  or amount of Venofer® needed [ml] = number of blood units lost x 10
- *If the Hb level is reduced:* use the previous formula considering that the depot iron does not need to be restored.
  Iron to be replaced [mg] = body weight [kg] x 0.24 x (target Hb – actual Hb) [g/l]

e.g.: body weight 60 kg, Hb deficit = 10 g/l ⇒ iron to be replaced = 150 mg ⇒ 7.5 ml Venofer® needed

**Normal posology**
*Adults and the Elderly:*
5–10 ml Venofer® (100 to 200 mg iron) twice or three times a week depending on the haemoglobin level.
*Children:*
0.15 ml Venofer®/kg body weight (= 3 mg iron/kg bw) twice or three times a week depending on the haemoglobin level.

**Maximum tolerated single dose**
*Adults and the Elderly:*
*As injection:* 10 ml Venofer® (200 mg iron) injected in at least 10 minutes.
*As infusion:* if the clinical situation demands the single dose may be increased to 0.35 ml Venofer®/kg body weight (= 7 mg iron/kg bw) not exceeding 25 ml Venofer® (500 mg iron), diluted in 500 ml 0.9% NaCl infused over at least 3.5 hours, once a week.
*Children:*
0.35 ml Venofer®/kg body weight (= 7 mg iron/kg bw) diluted in NaCl 0.9% and infused over at least 3.5 hours, once a week.

**Contra-indications**
The use of Venofer® is contra-indicated in cases of:
- anaemia not caused by iron deficiency
- iron overload or disturbances in utilisation of iron
- known hypersensitivity to iron mono- or disaccharide complexes

**Special warnings and special precautions for use**
Venofer® should only be administered where the indication is confirmed by appropriate investigations (e.g. serum ferritin, or haemoglobin (Hb), or haematocrit, or erythrocyte count, or red cell indices – MCV, MCH, MCHC).
Parenterally administered iron preparations can cause allergic or anaphylactoid reactions. In the case of a mild allergic reaction, antihistamines should be administered; in the case of a serious anaphylactic reaction adrenaline should be administered immediately. Patients with bronchial asthma, with low iron

Si la dose totale nécessaire dépasse la dose unique maximale, l'administration doit être fractionnée. Si aucune réponse hématologique n'est observée après 1 à 2 semaines, le diagnostic initial doit être reconsidéré.

**Calcul de la dose totale nécessaire en cas de substitution de fer faisant suite à une hémorragie et/ou destinée à soutenir une transfusion autologue programmée**
La dose de Venofer® nécessaire pour compenser le déficit martial est calculée en utilisant les formules suivantes:
- *Si la quantité de sang perdu est connue:* Sachant que l'administration intraveineuse de 200 mg de fer (=10 ml de Venofer®) produit une augmentation de la concentration en hémoglobine qui est équivalente à celle produite par l'administration d'une unité de sang (de 400 ml contenant 150 g/l d'Hb), on en déduit:
  Quantité de fer totale à remplacer [en mg] = nombre d'unités de sang perdu x 200, d'où quantité totale de Venofer® à administrer = nombre d'unités de sang perdu x 10.
- *Si la concentration en hémoglobine est réduite:* On utilise la formule générale en considérant que dans ce cas, les réserves de fer n'ont pas besoin d'être restaurées. D'où:
  Quantité de fer totale à remplacer [mg] = poids corporel [kg] x 0,24 x (Hb cible - Hb actuelle) [g/l]

Exemple: pour un poids corporel de 60 kg et un déficit en hémoglobine de 10 g/l la quantité de fer qui doit être remplacée = 150 mg, c.-à-d. 7,5 ml de Venofer® sont nécessaires dans ce cas

**Posologie usuelle**
*Adultes:*
5 à 10 ml de Venofer® (100 à 200 mg de fer) administrés deux à trois fois par semaine en fonction du taux d'hémoglobine.
*Enfants:*
0,15 ml de Venofer®/kg/jour (= 3 mg de fer/kg ) deux à trois fois par semaine en fonction du taux d'hémoglobine.

**Dose unique maximale tolérée**
*Adultes et personnes âgées:*
*En injection:* 10 ml de Venofer® (200 mg de fer) injectés en 10 minutes au moins.
*En perfusion:* si la situation clinique l'exige, la dose unique peut être portée à 0,35 ml de Venofer®/kg (7 mg de fer/kg ) sans dépasser 25 ml de Venofer® (500 mg de fer) dilués dans 500 ml de NaCl 0,9% et perfusés en 3 heures et ½ au moins, une fois par semaine.
*Enfants:*
0,35 ml de Venofer®/kg (7 mg de fer/kg) dilués dans du NaCl 0,9%, perfusés en 3 heures et ½ au moins, une fois par semaine.

**Contre-indications**
Venofer® est contre-indiqué en cas de:
- anémie dont la cause n'est pas un déficit martial
- surcharge martiale ou troubles de l'utilisation du fer
- hypersensibilité connue aux complexes mono ou disaccharidiques du fer

**Mises en garde et précautions particulières d'emploi**
Venofer® ne doit être administré que si l'indication a été confirmée par des analyses de laboratoire appropriées (par ex. ferritinémie, hémoglobinémie, hématocrite, comptage des érythrocytes et indices cellulaires: VGM, TCMH et CCMH).
Les préparations à base de fer administrées par voie parentérale peuvent causer des réactions allergiques ou anaphy-

Si la dosis total necesaria sobrepasa la máxima dosis única permitida, se debe distribuir la administración. Si no se observa una respuesta de los parámetros hematológicos después de 1 a 2 semanas, se debe revisar el diagnóstico inicial.

**Calculación de la dosificación para el reemplazo de hierro secundario a la pérdida de sangre y para el sostenimiento de la donación autóloga de sangre**
La dosis de Venofer® requerida para compensar el deficit de hierro se calcula según las fórmulas siguientes:
- *si la cantidad de la pérdida de sangre es conocida:* La administración de 200 mg de hierro i.v. (= 10 ml de Venofer®) resulta en un aumento en hemoglobina equivalente a 1 unidad de sangre (= 400 ml con un contenido de 150 g/l Hb).
  Hierro a ser reemplazado [mg] = número de unidades de sangre perdida x 200 o
  cantidad de Venofer® requerida [ml] = número de unidades de sangre perdida x 10
- *si el nivel de Hb es reducido:* usar la fórmula previa considerando que el hierro de reserva no necesita ser restaurado.
  Hierro a ser reemplazado [mg] = peso corporal [kg] x 0,24 x (Hb teórica – Hb real) [g/l]

p.ej.: peso corporal 60 kg, deficit Hb 10 g/l ⇒ hierro a ser reemplazado = 150 mg ⇒ 7,5 ml Venofer® requeridos

**Posología normal**
*Niños:*
0,15 ml de Venofer®/ kg peso corporal (= 3 mg de hierro/kg pc) dos o tres veces a la semana dependiendo del nivel de hemoglobina.
*Adultos y ancianos:*
5–10 ml de Venofer® (100 a 200 mg de hierro) dos o tres veces a la semana dependiendo del nivel de hemoglobina.

**Máxima dosis única tolerada**
*Niños:*
0,35 ml de Venofer®/kg peso corporal (= 7 mg de hierro/kg pc) diluidos en NaCl al 0,9% e infundido en 3,5 horas como mínimo, una vez a la semana.
*Adultos y ancianos:*
*Como inyección:* 10 ml de Venofer® (200 mg de hierro) inyectado en 10 minutos como mínimo.
*Como infusión:* si la situación clínica lo exige se puede elevar la dosis única a 0,35 ml de Venofer®/kg peso corporal (= 7 mg de hierro/kg pc) sin exceder los 25 ml de Venofer® (500 mg de hierro) diluidos en 500 ml de NaCl al 0,9% e infundido en 3,5 horas como mínimo, una vez a la semana.

**Contraindicaciones**
El uso de Venofer® es contraindicado en casos de:
- anemia no causada por deficiencia de hierro
- sobrecarga de hierro o trastornos en el aprovechamiento del hierro
- hipersensibilidad conocida contra complejos de hierro y mono o disacáridos

**Avisos especiales y precauciones especiales para el uso**
Venofer® sólo debe administrarse cuando la indicación es confirmada por investigaciones adecuadas (p.ej. nivel de ferritina sanguínea, o hemoglobina (Hb), o hematocrito, o recuento de eritrocitos o los índices de celulas rojas – MCV, MCH y MCHC).
Preparados de hierro administrados por vía parenteral pueden causar reacciones alergicas o anafilácticas. En caso de re-

binding capacity and/or folic acid deficiency are particularly at risk of an allergic or anaphylactic reaction.
Venofer® must be used with care in patients with serious hepatic dysfunction, an acute infection, a history of allergy or chronic infection.
Hypotensive episodes may occur if injection is administered too rapidly.
Beware of paravenous leakage. In cases of inadvertent paravenous leakage, proceed as follows: if the needle is still inserted, rinse with a small amount of 0.9% sodium chloride solution. In order to accelerate the elimination of the iron, instruct the patient to treat the point of injection topically with a mucopolysaccharid gel or ointment. Administer the gel or ointment gently (cave massage) in order to avoid further spreading of the iron.
Parenterally administered iron preparations can unfavourably influence the course of infections in children.

**Interaction with other medicaments and other forms of interaction**
As with all parenteral iron preparations, Venofer® should not be administered concomitantly with oral iron preparations since the absorption of oral iron is reduced. Therefore an oral iron therapy should at least be started 5 days after the last injection.

**Pregnancy and lactation**
Use of parenteral iron preparations during the first three months has to be discouraged. During the second and third term the application has to be done with caution.
It is not known if an increased excretion of iron in the breast milk takes place after parenteral administration of iron.

**Effects on ability to drive and use machines**
Presumed to be safe and unlikely to produce an effect.

**Undesirable effects**
Very rarely allergic anaphylactic like reactions may occur.
Occasionally the following undesirable effects have been reported with a frequency of ≥ 1%: metallic taste, headache, nausea, vomiting and hypertension.
Less frequently paresthesia, abdominal disorders, muscular pain, fever, urticaria, flushing, oedema of the extremities and anaphylactoid (pseudoallergic) reactions have been reported. In the region of the punctured vein, phlebitis and venous spasm have been observed.

**Symptoms and treatment of overdose**
*General:* Fatal courses after overdosage with parenteral iron preparations are reported.
Symptoms that could be expected: nausea, vomiting, diarrhoea, stomach pain and lethargy.
In serious cases, the following symptoms could be expected: hyperglycaemia, leukocytosis, metabolic acidosis, a progressive collapse of the circulation (hypotension, tachycardia), convulsions and coma. After 12–48 hours, necrosis of the tubulus and liver cells could be possible.
Treatment should be commenced by administering deferoxamine, if the following symptoms occur within 6 hours of the overdose:
– vomiting, diarrhoea, blood glucose > 8.3 mmol (1.5 g/l) and leucocytes > 15 x $10^9$ per litre.
If the patient is not in a state of shock, 1–2 g of deferoxamine (children 20 mg/kg bw) should be given intramuscularly every 4–12 hours. If the patient is in shock, an initial dose of 1 g of deferoxamine should be intravenously infused at a maximum speed of 15 mg/kg bw per hour. In both cases the maximum dose of deferoxamine should be 6 g per 24 hours in adults and 180 mg/kg bw per 24 hours for children.
In the case of renal insufficiency, haemodialysis will be necessary whereby the deferoxamine-iron complex (ferrioxamine) is effectively removed by dialysis.

## PHARMACOLOGICAL PROPERTIES
The polynuclear iron(III)-hydroxide cores are superficially surrounded by a large number of non-covalently bound sucrose molecules resulting in a complex whose molecular mass is approximately Mw 43 kD. This is sufficiently large to prohibit renal elimination. The resulting complex is stable and does not release ionic iron under physiological conditions. The iron in the polynuclear cores is bound in a similar structure as in the case of physiologically occurring ferritin.

**Pharmacodynamic properties**
Administration of Venofer® causes physiological changes which involve the uptake of iron.

lactoïdes. En cas de réaction allergique modérée, administrer des antihistaminiques. En cas de réaction anaphylactique grave, administrer de l'adrénaline immédiatement.
Les patients asthmatiques ou ayant une capacité totale de fixation du fer réduite et/ou présentant un déficit en acide folique sont particulièrement exposés au risque d'une réaction allergique ou anaphylactique.
Venofer® doit être utilisé avec précaution chez les patients atteints de graves troubles hépatiques, d'infections aiguës ou chroniques ou chez les sujets ayant des antécédents allergiques.
Des épisodes hypotensifs peuvent apparaître si l'injection est effectuée trop rapidement.
Attention à l'administration périveineuse de Venofer®. En cas d'injection périveineuse accidentelle, procéder comme suit: si l'aiguille est encore en place, rincer avec une petite quantité de NaCl 0,9%. Afin d'accélérer l'élimination du fer, appliquer localement un gel ou une crème à base de mucopolysaccharide en prenant soin d'éviter tout massage pour ne pas causer de plus ample diffusion du fer et montrer au patient comment procéder pour poursuivre ce traitement.
Chez l'enfant, les produits à base de fer administrés par voie parentérale peuvent aggraver les infections.

**Interactions avec d'autres médicaments et autres formes d'interactions**
Tous les produits à base de fer pour usage parentéral peuvent diminuer l'absorption du fer oral. C'est pourquoi Venofer® ne devrait pas être administré en même temps qu'un traitement à base de fer per os. Ainsi, il faut attendre au moins 5 jours après la dernière injection de Venofer® avant d'initier une thérapie martiale per os.

**Grossesse et allaitement**
L'usage de fer parentéral pendant les trois premiers mois de grossesse doit être découragé. Pendant le deuxième et troisième trimestre son utilisation doit être faite avec précautions.
On ne sait pas si une excrétion accrue de fer dans le lait maternel a lieu après administration de fer parentéral.

**Effets sur l'aptitude à conduire des véhicules et à utiliser des machines**
Présumé sûr et vraisemblablement sans effets.

**Effets indésirables**
Exceptionnellement, des réactions de type anaphylactique peuvent être observées.
Occasionnellement, les effets indésirables suivants sont été rapportés avec une fréquence ≥ 1%: goût métallique, maux de tête, nausées, vomissements et hypotension.
Plus rarement: paresthésie, troubles abdominaux, douleurs musculaires, fièvres, urticaires, bouffées de chaleur, œdèmes des extrémités, réactions anaphylactoïdes (pseudoallergiques) et au site d'injection: phlébites et spasmes veineux ont été rapportés.

**Symptômes et traitement en cas de surdosage**
*Aspect général:* des surdosages avec une issue fatale ont été rapportés avec des préparations à base de fer parentéral. Les symptômes attendus seraient les suivants: nausées, vomissements, diarrhées, douleurs gastriques et léthargie.
Dans les cas graves les symptômes attendus seraient les suivants: hyperglycémie, leucocytose, acidose métabolique, collapsus circulatoire progressif (hypotension, tachycardie), convulsions et coma. Après 12 à 48 heures des nécroses des tubules et des cellules hépatiques seraient possibles.
Le traitement devrait commencer par l'administration de deferoxamine, si les symptômes suivants apparaissent dans les 6 heures: vomissements, diarrhées, glycémie > 8,3 mmol (1,5 g/l) et leucocytes > 15 x $10^9$/l.
Si le patient n'est pas en état de choc, 1 à 2 g de deferoxamine (enfant 20 mg/kg) devraient être administrés intramusculairement toutes les 4 à 12 heures. Si le patient est choqué une dose initiale de 1 g de deferoxamine devrait être perfusée à une vitesse maximum de 15 mg/kg/heure. Dans les deux cas la dose maximum ne devrait pas excéder 6 g/24 heures chez l'adulte et 180 mg/kg/24 heures chez l'enfant.
Dans le cas d'insuffisance rénale, l'hémodialyse est nécessaire car c'est un moyen efficace d'éliminer le complexe deferoxamine-fer (ferrioxamine).

## PROPRIÉTÉS PHARMACOLOGIQUES:
Les noyaux d'hydroxyde de fer(III) sont entourés par un grand nombre de molécules de sucrose liées par des liaisons non-covalentes, formant un complexe d'un poids moléculaire d'approximativement 43 kD. Ceci est suffisamment important pour empêcher toute élimination rénale. Le complexe obtenu est stable et ne libère pas de fer ionique dans les conditions physiologiques. Le fer dans les noyaux est lié dans une structure similaire à celle de la ferritine physiologique.

acciones alergicas leves, se debe administrar antihistamínicos; en caso de una reacción anafiláctica seria se debe administrar adrenalina inmediatamente. Pacientes con asma bronquial, con capacidad baja de fijar hierro y/o deficiencia de ácido fólico corren particularmente riesgo de padecer una reacción alergica o anafiláctica.
Venofer® tiene que ser usado con cuidado en pacientes con disfunción hepática seria, una infección aguda, una historia de alergia o infección crónica.
Pueden ocurrir episodios hipotensivos si la inyección es administrada demasiado rapida.
Cuid. con pérdida paravenosa. En casos de paravenosa inadvertida, se debe proceder del modo siguiente: si la aguja está todavía colocada, lavar con una pequeña cantidad de solución de cloruro sódico al 0,9%. Para acelerar la eliminación del hierro, se debe instruir el paciente de tratar el punto de inyección topicamente con un gel o una pomada mucopolisacárida. Administrar el gel o la pomada suavemente (evitar masaje) para evitar mas distribución del hierro.
Preparados de hierro administrados por vía parenteral pueden influir desfavorablemente el curso de infecciones en niños.

**Interacciones con otros medicamentos y otras formas de interacciones**
Como con todos los preparados parenterales de hierro, Venofer® no debe administrarse concomitantemente con preparados orales de hierro ya que la absorción del hierro oral es reducida. Por eso un tratamiento oral de hierro debería iniciarse como mínimo 5 días después de la última inyección.

**Embarazo y lactancia**
Se desaconseja el uso de preparados parenterales de hierro durante los primeros tres meses. La aplicación durante el segundo y el tercero trimestre debe hacerse con cuidado.
Se desconoce si en la leche materna ocurre una elevada excreción de hierro después de la administración de hierro por vía parenteral.

**Efectos en la capacidad de conducir y usar maquinas**
Presumido de ser seguro y no probable de producir un efecto.

**Efectos no deseados**
Muy raramente pueden ocurrir reacciones parecidas a la anafilaxis.
Ocasionalmente se reportaron los siguientes efectos no deseados con una frecuencia de ≥ 1%: sabor metalico, dolor de cabeza, náusea, fecaloideo y hipotensión. Con menos frecuencia se reportaron parestesia, enfermedades abdominales, dolores musculares, fiebre, urticaria, sofoco, acroedema y reacciones anafilactoides (pseudoalérgicas). En la zona de la vena pinchada se observaron flebitis y espasmo venoso.

**Síntomas y tratamiento de hiperdosificación**
*General:* Se reportaron cursos fatales después de hiperdosificación con preparados parenterales de hierro.
Síntomas que son de esperar: náusea, fecaloideo, diarres, dolores de estómago y letargo.
En casos series los síntomas siguientes son de esperar: hiperglucemia, leucocitosis, acidosis metabólica, un colapso progresivo de la circulación (hipotensión, taquicardia), convulsione y coma. Después de 12 a 48 horas, necrosis de las celulas del túbulo y del hígado puede ser posible.
Se debe comenzar un tratamiento administrando deferoxamina, si entre 6 horas después de la hiperdosificación ocurren los síntomas siguientes:
– fecaloideo, diarres, mas de 8,3 µmol (1,5 g/l) glucosa sanguínea y mas de 15 x $10^9$ leucocitos por litro.
Si el paciente no está en estado de shock, se debe aplicar 1 a 2 g de deferoxamina (niños 20 mg/kg peso corporal) por vía intramuscular cada 4 a 12 horas. Si el paciente está en shock, se debe infundir una dosis inicial de 1 g de deferoxamina por vía intravenosa en una velocidad máxima de 15 mg/kg pc por hora. En los dos casos la dosis máxima de deferoxamina debería ser 6 g por 24 horas en adultos y 180 mg/kg pc por 24 horas para niños.
En caso de insuficiencia renal, será necesaria la hemodiálisis en la cuál el complejo de deferoxamina e hierro (ferrioxamina) es removido con efectividad por diálisis.

## PROPIEDADES FARMACOLÓGICAS
Las cortezas polinucleares de hidróxido de hierro están rodeadas por la superficie por un gran numero de moléculas de sacarosa fijadas de forma no covalente, resultando en un complejo con un peso molecular de aproximadamente Mw 43 kD. Eso es lo grande suficiente para prohibir la eliminación renal. El complejo resultante es estable y no libra hierro iónico en condiciones fisiológicas. El hierro en las cortezas polinucleares es fijado en una estructura similar a la de la ferritina que se halla fisiologicamente.

**Pharmacokinetic properties**
The pharmacokinetics of Iron(III)-Hydroxide Sucrose Complex was investigated after intravenous injection of a single dose containing 100 mg Fe(III) in healthy volunteers. The maximum iron levels, averaging 538 µmol/l, are obtained 10 minutes after injection. The volume of distribution of the central compartment corresponds in good agreement to the volume of serum (approx. 3 l).
The iron injected is quickly cleared from the serum, the terminal half-life is approx. 6 h. The volume of distribution at steady state is about 8 l, which indicates a low iron distribution in the body water. Due to the lower stability of Iron(III)-Hydroxide Sucrose Complex in comparison to transferrin, a competitive exchange of iron to transferrin was observed. This results in a iron transport of approx. 31 mg Fe(III)/24 h.
Renal elimination of iron, occurring in the first 4 h after injection, corresponds to less than 5% of the total body clearance (approx. 20 ml/min). After 24 h the serum levels of iron are reduced to the predose iron levels and about 75% of the dosage of sucrose is excreted.

**Preclinical 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**
Venofer® 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**
Protect from light at a temperature between 4 and 25°C. Protect from excessive heat and do not freeze. Incorrect storage can lead to formation of sediments visible to the unaided eye.

**Nature and contents of container**
Type I glass ampoules of 1 and 5ml extractable volume (Ph. Eur.).

**Instructions for use/handling**
Ampoules should be visually inspected for sediments and damage before use. Only those with sediment free and homogeneous solution must be used.
Once opened, Venofer® should be administered immediately.
Venofer® diluted with 0.9% sodium chloride solution should be used within 12 hours if stored between 4 and 25°C.

**Package form**
Ampoules (5 ml) containing 100 mg of iron: 5 and 50
Ampoules (1 ml) containing 20 mg of iron: 5

Vifor (International) Inc.
P.O. Box, 9001 St.Gallen/Switzerland

**Propriétés pharmacodynamiques**
L'administration de Venofer® conduit à des modifications physiologiques impliquant la capture du fer.

**Propriétés pharmacocinétiques**
Après l'injection intraveineuse d'une dose unique de Venofer® contenant 100 mg de fer(III) chez des volontaires sains, la concentration maximale de fer (538 µmol/l en moyenne) est obtenue en 10 minutes. Le volume de distribution, de l'ordre de 3 litres est proche de celui du sérum.
Le fer injecté est rapidement éliminé du sérum, avec une demi-vie terminale d'approximativement 6 heures. Le volume de distribution au point d'équilibre est d'à peu près 8 l, ce qui indique une faible distribution du fer dans les liquides de l'organisme.
Etant donnée la moindre stabilité du complexe par rapport à la transferrine physiologique, un échange compétitif de fer avec celle-ci a été observé avec pour résultat, un transport de fer d'approximativement 31 mg de fer(III) par 24 heures.
La très faible élimination rénale du fer qui a lieu au cours des 4 premières heures après l'injection correspond à moins de 5% de la clairance corporelle totale (approx. 20 ml/min.). Après 24 heures, le fer sérique revient à sa valeur d'avant l'injection et 75% environ du saccharose injecté est éliminé.

**Données de sécurité préclinique**
Chez les animaux utilisés en expérimentation, une toxicité n'a été observée qu'à des doses suffisamment élevées par rapport aux doses maximales préconisées chez l'homme. Les données recueillies chez l'animal ne montrent pas de risques potentiels pour l'être humain.

**DONNÉES PHARMACEUTIQUES**
**Liste des excipients:**
Eau pour préparations injectables et NaOH.

**Incompatibilités**
Venofer® ne doit être dilué que dans du NaCl 0,9% et ne doit être mélangé avec aucun autre agent.

**Durée de conservation**
Voir date de péremption.

**Précautions particulières de conservation**
Stocker à une température comprise entre 4 et 25°C à l'abri de la lumière. Protéger de toute source de chaleur et ne pas congeler. Un stockage incorrect peut conduire à la formation de sédiments visibles à l'œil nu.

**Nature et contenance du récipient**
Ampoule en verre de type I, ayant un volume extractible de 1 et 5 ml (Ph. Eur.).

**Mode d'emploi, instructions concernant la manipulation**
Il est important d'inspecter les ampoules avant l'usage afin de détecter d'éventuels dommages et sédiments. Seules celles qui contiennent une solution homogène et exempte de sédiments, doivent être utilisées.
Toute ampoule de Venofer® ouverte doit être administrée immédiatement.
Toute solution obtenue par dilution de Venofer® dans du NaCl 0,9% doit être utilisée dans les 12 heures si elle est conservée entre 4 et 25°C.

**Présentations**
Ampoules (de 5 ml) contenant 100 mg de fer: 5 et 50
Ampoules (de 1 ml) contenant 20 mg de fer: 5

**Propiedades farmacodinámicas**
La administración de Venofer® causa cambios fisiológicos que envuelven la asimilación del hierro.

**Propiedades farmacocinéticas**
Las farmacocinética del complejo de sacarosa e hidróxido férrico fue investigado después de la inyección intravenosa de una dosis única conteniendo 100 mg de Fe(III) en voluntarios sanos. Los máximos niveles de hierro, promedio de 538 µmol/l, se obtenieron 10 minutos después de la inyección. El volumen de distribución del compartimento central corresponde de buena conformidad con el volumen del suero (aprox. 3 l).
El hierro inyectado es rapidamente aclarado por el suero, la semidesintegración terminal es aprox. de 6 horas. El volumen de distribución en estado estable es aprox. de 8 l; lo que significa que existe una escasa distribución de hierro en la agua corporal. Debido a la estabilidad inferior del complejo de sacarosa e hidróxido férrico en comparación con la transferrina, se observó un intercambio competitivo de hierro a la transferrina. Eso resulta en un transporte de hierro de aprox. 31 mg Fe(III)/24 horas. La eliminación renal del hierro, que ocurre en las primeras 4 horas posteriores a la inyección, corresponde a menos del 5% del aclaramiento total del cuerpo (aprox. 20ml/min). Después de 24 horas la sideremia es reducida a los niveles de hierro antes de la dosis y aprox. 75% del dosage de la sacarosa es excretada.

**Datos preclínicales de seguridad**
La toxicidad en animales experimentales solo se observó en dosages suficientemente altos comparados con el máximo dosage humano. Los datos de los animales experimentales no muestran un riesgo de seguridad para el ser humano.

**PARTICULARES FARMACÉUTICOS**
**Lista de excipientes**
Agua para inyectables e hidróxido sódico.

**Incompatibilidades**
Venofer® sólo debe mezclarse con solución de cloruro sódico al 0,9%. No se debe añadir otros agentes terapéuticos.

**Fecha de expiración**
Observar fecha de vencimiento.

**Precauciones especiales para el almacenamiento**
Proteger de la luz a una temperatura entre 4 y 25 °C. Proteger de calor excesivo y no congelar. El almacenamiento incorrecto puede llegar a formar sedimentos visibles al ojo no asistido.

**Naturaleza y contenido del recipiente**
Ampollas de vidrio del tipo I de 1 ml y 5 ml de volumen extractable (Ph. Eur.).

**Instrucciones para el uso/trato**
Las ampollas deben ser inspeccionadas para sedimentos y para daños antes del uso. Solo se pueden usar aquellas con solución homogénea y carente de sedimentos.
Una vez abierto, Venofer® debe administrarse inmediatamente
Venofer® diluido con solución de cloruro sódico al 0,9% debe ser usado entre 12 horas si es almacenado entre 4 y 25°C.

**Forma de envase**
Ampollas (5 ml) conteniendo 100 mg de hierro: 5 y 50
Ampollas (1 ml) conteniendo 20 mg de hierro: 5