Appendix F: Iron Therapeutic Product Package Inserts

Ferrlecit®, ferric gluconate

Venofer®, iron sucrose

Ferrlecit

(sodium ferric gluconate complex in sucrose injection)

DESCRIPTION

Ferrlecit® (sodium ferric gluconate complex in sucrose injection) is a stable macromolecular complex with an apparent molecular weight on gel chromatography of 289,000 – 440,000 daltons. The macromolecular complex is negatively charged at alkaline pH and is present in solution with sodium cations. The product has a deep red color indicative of ferric oxide linkages.

The structural formula is considered to be $[NaFe_2O_3(C_6H_{11}O_7)(C_{12}H_{22}O_{11})]_{8.5\pm1.0}$.

Each ampule of 5 mL of Ferrlecit® for intravenous injection contains 62.5 mg (12.5 mg/mL) of elemental iron as the sodium salt of a ferric ion carbohydrate complex in an alkaline aqueous solution with approximately 20% sucrose w/v (195 mg/mL) in water for injection, pH 7.7-9.7.

Each mL contains 9 mg of benzyl alcohol as an inactive ingredient.

Therapeutic Class: Hematinic

CLINICAL PHARMACOLOGY

Ferrlecit® is used to replete the total body content of iron. Iron is critical for normal hemoglobin synthesis to maintain oxygen transport. Additionally, iron is necessary for metabolism and various enzymatic processes.

The total body iron content of an adult ranges from 2 to 4 grams. Approximately 2/3 is in hemoglobin and 1/3 is in reticuloendothelial (RE) storage (bone marrow, spleen, liver) bound to intracellular ferritin. The body highly conserves iron (daily loss of 0.03%) requiring supplementation of about 1 mg/day to replenish losses in healthy, non-menstruating adults. The etiology of iron deficiency in hemodialysis patients is varied and can include blood loss and/or increased iron utilization (e.g., from epoetin therapy). The administration of exogenous epoetin increases red blood cell production and iron utilization. The increased iron utilization and blood losses in the hemodialysis patient may lead to absolute or functional iron deficiency. Iron deficiency is absolute when hematological indicators of iron stores are low. Patients with functional iron deficiency do not meet laboratory criteria for absolute iron deficiency but demonstrate an increase in hemoglobin/hematocrit or a decrease in epoetin dosage with stable hemoglobin/hematocrit when parenteral iron is administered.

Pharmacokinetics

Multiple sequential single dose intravenous pharmacokinetic studies were performed on 14 healthy iron-deficient volunteers. Entry criteria included hemoglobin ≥10.5 gm/dL and transferrin saturation ≤15% (TSAT) or serum ferritin value ≤20 ng/mL. In the first stage, each subject was randomized 1:1 to undiluted Ferrlecit® injection of either 125 mg/hr or 62.5 mg/0.5 hr (2.1 mg/min). Five days after the first stage, each subject was re-randomized 1:1 to undiluted Ferrlecit® injection of either 125 mg/7 min or 62.5 mg/4 min (>15.5 mg/min).

Peak drug levels (C_{max}) varied significantly by dosage and by rate of administration with the highest C_{max} observed in the regimen in which 125 mg was administered in 7 minutes (19.0 mg/L). The initial volume of distribution (V_{1ss}) of 6 L corresponds well to calculated blood volume. V_{1ss} did not vary by dosage or rate of administration. The terminal elimination half-life (λ_z-HL) for drug bound iron was approximately 1 hour. λ_z-HL varied by dose but not by rate of administration. The shortest value (0.85 h) occurred in the 62.5 mg/4 min regimen; the longest value (1.45 h) occurred in the 125 mg/7 min regimen. Total clearance of Ferrlecit® was 3.02 to 5.35 L/h. There was no significant variation by rate of administration. The AUC for Ferrlecit® bound iron varied by dose from 17.5 mg-h/L (62.5 mg) to 35.6 mg-h/L (125 mg). There was no significant variation by rate of administration. Approximately 80% of drug bound iron was delivered to transferrin as a mononuclear ionic iron species within 24 hours of administration in each dosage regimen. Direct movement of iron from Ferrlecit® to transferrin was not observed. Mean peak transferrin saturation did not exceed 100% and returned to near baseline by 40 hours after administration of each dosage regimen.

Pediatrics: Single dose intravenous pharmacokinetic analyses were performed on 48 iron-deficient pediatric hemodialysis patients. Twenty-two patients received 1.5 mg/kg Ferrlecit® and 26 patients received 3.0 mg/kg Ferrlecit® (maximum dose 125 mg). The mean C_{max}, $AUC_{0-\infty}$, and terminal elimination half-life values for the 22 patients who received a 1.5 mg/kg dose were 12.9 mg/L, 95.0 mg•hr/L, and 2.0 hours, respectively. The mean C_{max}, $AUC_{0-\infty}$, and the terminal elimination half-life values for the 26 patients who received a 3.0 mg/kg dose were 22.8 mg/L, 170.9 mg•hr/L, and 2.5 hours, respectively.

In vitro experiments have shown that less than 1% of the iron species within Ferrlecit® can be dialyzed through membranes with pore sizes corresponding to 12,000 to 14,000 daltons over a period of up to 270 minutes. Human studies in renally competent patients suggest the clinical insignificance of urinary excretion.

Drug-drug Interactions: Drug-drug interactions involving Ferrlecit® have not been studied. However, like other parenteral iron preparations, Ferrlecit® may be expected to reduce the absorption of concomitantly administered oral iron preparations.

CLINICAL STUDIES

Two clinical studies (Studies A and B) were conducted in adults and one clinical study was conducted in pediatric patients (Study C) to assess the efficacy and safety of Ferrlecit®.

Study A

Study A was a three-center, randomized, open-label study of the safety and efficacy of two doses of Ferrlecit® administered intravenously to iron-deficient hemodialysis patients. The study included both a dose-response concurrent control and an historical control. Enrolled patients received a test dose of Ferrlecit® (25 mg of elemental iron) and were then randomly assigned to receive Ferrlecit® at cumulative doses of either 500 mg (low dose) or 1000 mg (high dose) of elemental iron. Ferrlecit® was given to both dose groups in eight divided doses during sequential dialysis sessions (a period of 16 to 17 days). At each dialysis session, patients in the low-dose group received Ferrlecit® 62.5 mg of elemental iron over 30 minutes, and those in the high-dose group received Ferrlecit® 125 mg of elemental iron over 60 minutes. The primary endpoint was the change in hemoglobin from baseline to the last available observation through Day 40.

Eligibility for this study included chronic hemodialysis patients with a hemoglobin below 10 g/dL (or hematocrit at or below 32%) and either serum ferritin below 100 ng/mL or transferrin saturation below 18%. Exclusion criteria included significant underlying disease or inflammatory conditions or an epoetin requirement of greater than 10,000 units three times per week. Parenteral iron and red cell transfusion were not allowed for two months before the study. Oral iron and red cell transfusion were not allowed during the study for Ferrlecit®-treated patients.

The historical control population consisted of 25 chronic hemodialysis patients who received only oral iron supplementation for 14 months and did not receive red cell transfusion. All patients had stable epoetin doses and hematocrit values for at least two months before initiation of oral iron therapy.

The evaluated population consisted of 39 patients in the low-dose Ferrlecit® (sodium ferric glucouate complex in sucrose injection) group (50% female, 50% male; 74% white, 18% black, 5% Hispanic, 3% Asian; mean age 54 years, range 22-83 years), 44 patients in the high-dose Ferrlecit® group (50% female, 48% male, 2% unknown; 75% white, 11% black, 5% Hispanic, 7% other, 2% unknown; mean age 56 years, range 20-87 years), and 25 historical control patients (68% female, 32% male; 40% white, 32% black, 20% Hispanic, 4% Asian, 4% unknown; mean age 52 years, range 25-84 years).

The mean baseline hemoglobin and hematocrit were similar between treatment and historical control patients: 9.8 g/dL and 29% and 9.6 g/dL and 29% in low- and high-dose Ferrlecit®-treated patients, respectively, and 9.4 g/dL and 29% in historical control patients. Baseline serum transferrin saturation was 20% in the low-dose group, 16% in the high-dose group, and 14% in the historical control. Baseline serum ferritin was 106 ng/mL in the low-dose group, 88 ng/mL in the high-dose group, and 606 ng/mL in the historical control.

Patients in the high-dose Ferrlecit® group achieved significantly higher increases in hemoglobin and hematocrit than either patients in the low-dose Ferrlecit® group or patients in the historical control group (oral iron). Patients in the low-dose Ferrlecit® group did not achieve significantly higher increases in hemoglobin and hematocrit than patients receiving oral iron. See Table 1.

TABLE 1
Hemoglobin, Hematocrit, and Iron Studies

Study A	Mean Change from Baseline to Two Weeks After Cessation of Therapy		
	Ferrlecit® 1000 mg IV (N=44)	Ferrlecit® 500 mg IV (N=39)	Historical Control Oral Iron (N=25)
Hemoglobin (g/dL)	1.1*	0.3	0.4
Hematocrit (%)	3.6*	1.4	0.8
Transferrin Saturation (%)	8.5	2.8	6.1
Serum Ferritin (ng/mL)	199	132	NA

*p<0.01 versus both the 500 mg group and the historical control group.

Study B

Study B was a single-center, non-randomized, open-label, historically-controlled, study of the safety and efficacy of variable, cumulative doses of intravenous Ferrlecit® in iron-deficient hemodialysis patients. Ferrlecit® administration was identical to Study A. The primary efficacy variable was the change in hemoglobin from baseline to the last available observation through Day 50.

Inclusion and exclusion criteria were identical to those of Study A as was the historical control population. Sixty-three patients were evaluated in this study: 38 in the Ferrlecit®-treated group (37% female, 63% male; 95% white, 5% Asian; mean age 56 years, range 22-84 years) and 25 in the historical control group (68% female, 32% male; 40% white, 32% black, 20% Hispanic, 4% Asian, 4% unknown; mean age 52 years, range 25-84 years).

Ferrlecit®-treated patients were considered to have completed the study per protocol if they received at least eight Ferrlecit® doses of either 62.5 mg or 125 mg of elemental iron. A total of 14 patients (37%) completed the study per protocol. Twelve (32%) Ferrlecit®-treated patients received less than eight doses, and 12 (32%) patients had incomplete information on the sequence of dosing. Not all patients received Ferrlecit® at consecutive dialysis sessions and many received oral iron during the study.

Cumulative Ferrlecit® Dose (mg of elemental iron)	62.5	250	375	562.5	625	750	1000	1125	1187.5
Patients (#)	1	1	2	1	10	4	12	6	1

Baseline hemoglobin and hematocrit values were similar between the treatment and control groups, and were 9.1 g/dL and 27.3%, respectively, for Ferrlecit®-treated patients. Serum iron studies were also similar between treatment and control groups, with the exception of serum ferritin, which was 606 ng/mL for historical control patients, compared to 77 ng/mL for Ferrlecit®-treated patients.

In this patient population, only the Ferrlecit®-treated group achieved significant increase in hemoglobin and hematocrit from baseline. This increase was significantly greater than that seen in the historical oral iron treatment group. See Table 2.

TABLE 2
Hemoglobin, Hematocrit, and Iron Studies

Study B	Mean Change from Baseline to One Month After Treatment	
	Ferrlecit® (N=38) change	Oral Iron (N=25) change
Hemoglobin (g/dL)	1.3a,b	0.4
Hematocrit (%)	3.8a,b	0.2
Transferrin Saturation (%)	6.7b	1.7
Serum Ferritin (ng/mL)	73b	-145

a - p<0.05 on group comparison by the ANCOVA method.

b - p<0.001 from baseline by the paired t-test method.

Study C

Study C was a multicenter, randomized, open-label study of the safety and efficacy of two Ferrlecit® dose regimens (1.5 mg/kg or 3.0 mg/kg of elemental iron) administered intravenously to 66 iron-deficient (transferrin saturation <20% and/or serum ferritin <100 ng/mL) pediatric hemodialysis patients, 6 to 15 years of age, inclusive, who were receiving a stable erythropoietin dosing regimen. Ferrlecit® at a dose of 1.5 mg/kg or 3.0 mg/kg (up to a maximum dose of 125 mg of elemental iron) in 25 mL 0.9% sodium chloride was infused intravenously over 1 hour during each hemodialysis session for eight sequential dialysis sessions. Thirty-two patients received the 1.5 mg/kg dosing regimen (47% male, 53% female; 66% Caucasian, 25% Hispanic, and 3% Black, Asian, or Other; mean age 12.3 years). Thirty-four patients received the 3.0 mg/kg dosing regimen (56% male, 44% female; 77% Caucasian, 12% Hispanic, and 9% Black, 3% Other; mean age 12.0 years).

The primary endpoint was the change in hemoglobin concentration from baseline to 2 weeks after last Ferrlecit® administration. Patients in both Ferrlecit® dose groups had statistically significant changes from baseline in hemoglobin concentrations (Table 3). There was no significant difference between the treatment groups. Statistically significant improvements in hematocrit, transferrin saturation, serum ferritin, and reticulocyte hemoglobin concentrations compared to baseline values were observed 2 weeks after the last Ferrlecit® infusion in both the 1.5 mg/kg and 3.0 mg/kg treatment groups (Table 3).

TABLE 3
Hemoglobin, Hematocrit, and Iron Status

Study C	Mean Change from Baseline to Two Weeks After Cessation of Therapy in Patients Completing Treatment	
	1.5 mg/kg Ferrlecit® (N=25)	3.0 mg/kg Ferrlecit® (N=32)
Hemoglobin (g/dL)	0.8*	0.9*
Hematocrit (%)	2.6*	3.0*
Transferrin Saturation (%)	5.5*	10.5*
Serum Ferritin (ng/mL)	192*	314*
Reticulocyte Hemoglobin Content (pg)	1.3*	1.2*

*p<0.03 versus the baseline values

The increased hemoglobin concentrations were maintained at 4 weeks after the last Ferrlecit® infusion in both the 1.5 mg/kg and the 3.0 mg/kg Ferrlecit® dose treatment groups.

INDICATIONS AND USAGE

Ferrlecit® (sodium ferric gluconate complex in sucrose injection) is indicated for treatment of iron deficiency anemia in adult patients and in pediatric patients age 6 years and older undergoing chronic hemodialysis who are receiving supplemental epoetin therapy.

CONTRAINDICATIONS

•All anemias not associated with iron deficiency.

•Hypersensitivity to Ferrlecit® or any of its inactive components.

•Evidence of iron overload.

WARNINGS

Hypersensitivity reactions have been reported with injectable iron products. See PRECAUTIONS.

PRECAUTIONS

General: Iron is not easily eliminated from the body and accumulation can be toxic. Unnecessary therapy with parenteral iron will cause excess storage of iron with consequent possibility of iatrogenic hemosiderosis. Iron overload is particularly apt to occur in patients with hemoglobinopathies and other refractory anemias. Ferrlecit® should not be administered to patients with iron overload. See OVERDOSAGE.

Hypersensitivity Reactions: Serious hypersensitivity reactions have been reported rarely in patients receiving Ferrlecit®. One case of a life-threatening hypersensitivity reaction has been observed in 1,097 patients who received a single dose of Ferrlecit® in a post-marketing safety study. Three serious hypersensitivity reactions have been reported from the spontaneous reporting system in the United States. See ADVERSE REACTIONS.

Hypotension: Hypotension associated with light-headedness, malaise, fatigue, weakness or severe pain in the chest, back, flanks, or groin has been associated with administration of intravenous iron. These hypotensive reactions are not associated with signs of hypersensitivity and have usually resolved within one or two hours. Successful treatment may consist of observation or, if the hypotension causes symptoms, volume expansion. See ADVERSE REACTIONS.

Carcinogenesis, mutagenesis, impairment of fertility: Long term carcinogenicity studies in animals were not performed. Studies to assess the effects of Ferrlecit® on fertility were not conducted. Ferrlecit® was not mutagenic in the Ames test and the rat micronucleus test. It produced a clastogenic effect in an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells.

Pregnancy Category B: Ferrlecit® was not teratogenic at doses of elemental iron up to 100 mg/kg/day (300 mg/m²/day) in mice and 20 mg/kg/day (120 mg/m²/day) in rats. On a body surface area basis, these doses were 1.3 and 3.24 times the recommended human dose (125 mg/day or 92.5 mg/m²/day) for a person of 50 kg body weight, average height and body surface area of 1.46 m². There were no adequate and well-controlled studies in pregnant women. Ferrlecit® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Ferrlecit® is administered to a nursing woman.

Pediatric Use: Ferrlecit® was shown to be safe and effective in pediatric patients ages 6 to 15 years (refer to CLINICAL STUDIES section). Safety and effectiveness in pediatric patients younger than 6 years of age have not been established.

Ferrlecit® contains benzyl alcohol and therefore should not be used in neonates.

Geriatric Use: Clinical studies of Ferrlecit® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In particular, 51/159 hemodialysis patients in North American clinical studies were aged 65 years or older. Among these patients, no differences in safety or efficacy as a result of age were identified. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Exposure to Ferrlecit® has been documented in over 1,400 patients on hemodialysis. This population included 1,097 Ferrlecit®-naïve patients who received a single-dose of Ferrlecit® in a placebo-controlled, cross-over, post-marketing safety study. Undiluted Ferrlecit® was administered over ten minutes (125 mg of Ferrlecit® at 12.5 mg/min). No test dose was used. From a total of 1,498 Ferrlecit®-treated patients in medical reports, North American trials, and post-marketing studies, twelve patients (0.8%) experienced serious reactions which precluded further therapy with Ferrlecit®.

Hypersensitivity Reactions: See PRECAUTIONS. In the single-dose, post-marketing, safety study one patient experienced a life-threatening hypersensitivity reaction (diaphoresis, nausea, vomiting, severe lower back pain, dyspnea, and wheezing for 20 minutes) following Ferrlecit® administration. Among 1,097 patients who received Ferrlecit® in this study, there were 9 patients (0.8%) who had an adverse reaction that, in the view of the investigator, precluded further Ferrlecit® administration (drug intolerance). These included one life-threatening reaction, six allergic reactions (pruritus x2, facial flushing, chills, dyspnea/chest pain, and rash), and two other reactions (hypotension and nausea). Another 2 patients experienced (0.2%) allergic reactions not deemed to represent drug intolerance (nausea/malaise and nausea/dizziness) following Ferrlecit® administration.

Seventy-two (7.0%) of the 1,034 patients who had prior iron dextran exposure had a sensitivity to at least one form of iron dextran (INFeD® or Dexferrum®). The patient who experienced a life-threatening adverse event following Ferrlecit® administration during the study had a previous severe anaphylactic reaction to dextran in both forms (INFeD® and Dexferrum®). The incidences of both drug intolerance and suspected allergic events following first dose Ferrlecit® administration were 2.8% in patients with prior iron dextran sensitivity compared to 0.8% in patients without prior iron dextran sensitivity.

In this study, 28% of the patients received concomitant angiotensin converting enzyme inhibitor (ACEi) therapy. The incidences of both drug intolerance or suspected allergic events following first dose Ferrlecit® administration were 1.6% in patients with concomitant ACEi use compared to 0.7% in patients without concomitant ACEi use. The patient with a life-threatening event was not on ACEi therapy. One patient had facial flushing immediately on Ferrlecit® exposure. No hypotension occurred and the event resolved rapidly and spontaneously without intervention other than drug withdrawal.

In multiple dose Studies A and B, no fatal hypersensitivity reactions occurred among the 126 patients who received Ferrlecit®. Ferrlecit®-associated hypersensitivity events in Study A resulting in premature study discontinuation occurred in three out of a total 88 (3.4%) Ferrlecit®-treated patients. The first patient withdrew after the development of pruritus and chest pain following the test dose of Ferrlecit®. The second patient, in the high-dose group, experienced nausea, abdominal and flank pain, fatigue and rash following the first dose of Ferrlecit®. The third patient, in the low-dose group, experienced a "red blotchy rash" following the first dose of Ferrlecit®. Of the 38 patients exposed to Ferrlecit® in Study B, none reported hypersensitivity reactions.

Many chronic renal failure patients experience cramps, pain, nausea, rash, flushing, and pruritus.

Three cases of serious hypersensitivity reactions have been reported from the spontaneous reporting system in the United States.

Hypotension: See PRECAUTIONS. In the single dose safety study, post-administration hypotensive events were observed in 22/1,097 patients (2%) following Ferrlecit® administration. Hypotension has also been reported following administration of Ferrlecit® in European case reports. Of the 226 renal dialysis patients exposed to Ferrlecit® and reported in the literature, 3 (1.3%) patients experienced hypotensive events, which were accompanied by flushing in two. All completely reversed after one hour without sequelae. Transient hypotension may occur during dialysis. Administration of Ferrlecit® may augment hypotension caused by dialysis.

Among the 126 patients who received Ferrlecit® in Studies A and B, one patient experienced a transient decreased level of consciousness without hypotension. Another patient discontinued treatment prematurely because of dizziness, lightheadedness, diplopia, malaise, and weakness without hypotension that resulted in a 3-4 hour hospitalization for observation following drug administration. The syndrome resolved spontaneously.

Adverse Laboratory Changes: No differences in laboratory findings associated with Ferrlecit® (sodium ferric gluconate complex in sucrose injection) were reported in North American clinical trials when normalized against a National Institute of Health database on laboratory findings in 1,100 hemodialysis patients.

Most Frequent Adverse Reactions: In the single-dose, post-marketing safety study, 11% of patients who received Ferrlecit® and 9.4% of patients who received placebo reported adverse reactions. The most frequent adverse reactions following Ferrlecit® were: hypotension (2%), nausea, vomiting and/or diarrhea (2%), pain (0.7%), hypertension (0.6%), allergic reaction (0.5%), chest pain (0.5%), pruritus (0.5%), and back pain (0.4%). Similar adverse reactions were seen following placebo administration. However, because of the high baseline incidence of adverse events in the hemodialysis patient population, insufficient number of exposed patients, and limitations inherent to the cross-over, single dose study design, no comparison of event rates between Ferrlecit® and placebo treatments can be made.

In multiple-dose Studies A and B, the most frequent adverse reactions following Ferrlecit® were:

Body as a Whole: injection site reaction (33%), chest pain (10%), pain (10%), asthenia (7%), headache (7%), abdominal pain (6%), fatigue (6%), fever (5%), malaise, infection, abscess, back pain, chills, rigors, arm pain, carcinoma, flu-like syndrome, sepsis.

Nervous System: cramps (25%), dizziness (13%), paresthesias (6%), agitation, somnolence.

Respiratory System: dyspnea (11%), coughing (6%), upper respiratory infections (6%), rhinitis, pneumonia.

Cardiovascular System: hypotension (29%), hypertension (13%), syncope (6%), tachycardia (5%), bradycardia, vasodilatation, angina pectoris, myocardial infarction, pulmonary edema.

Gastrointestinal System: nausea, vomiting and/or diarrhea (35%), anorexia, rectal disorder, dyspepsia, eructation, flatulence, gastrointestinal disorder, melena.

Musculoskeletal System: leg cramps (10%), myalgia, arthralgia.

Skin and Appendages: pruritus (6%), rash, increased sweating.

Genitourinary System: urinary tract infection.

Special Senses: conjunctivitis, abnormal vision, ear disorder.

Metabolic and Nutritional Disorders: hyperkalemia (6%), generalized edema (5%), leg edema, peripheral edema, hypoglycemia, edema, hypervolemia, hypokalemia.

Hematologic System: abnormal erythrocytes (11%), anemia, leukocytosis, lymphadenopathy.

Other Adverse Reactions Observed During Clinical Trials: In the single-dose post-marketing safety study in 1,097 patients receiving Ferrlecit®, the following additional events were reported in two or more patients: hypertonia, nervousness, dry mouth, and hemorrhage.

Pediatric Patients: In a clinical trial of 66 iron-deficient pediatric hemodialysis patients, 6 to 15 years of age, inclusive, who were receiving a stable erythropoietin dosing regimen, the most common adverse events, whether or not related to study drug, occurring in ≥ 5%, regardless of treatment group, were: hypotension (35%), headache (24%), hypertension (23%), tachycardia (17%), vomiting (11%), fever (9%), nausea (9%), abdominal pain (9%), pharyngitis (9%), diarrhea (8%), infection (8%), rhinitis (6%), and thrombosis (6%). More patients in the higher dose group (3.0 mg/kg) than in the lower dose group (1.5 mg/kg) experienced the following adverse events: hypotension (41% vs. 28%), tachycardia (21% vs. 13%), fever (15% vs. 3%), headache (29% vs. 19%), abdominal pain (15% vs. 3%), nausea (12% vs. 6%), vomiting (12% vs. 9%), pharyngitis (12% vs. 6%), and rhinitis (9% vs. 3%).

OVERDOSAGE

Dosages in excess of iron needs may lead to accumulation of iron in iron storage sites and hemosiderosis. Periodic monitoring of laboratory parameters of iron storage may assist in recognition of iron accumulation. Ferrlecit® should not be administered in patients with iron overload.

Serum iron levels greater than 300 µg/dL may indicate iron poisoning which is characterized by abdominal pain, diarrhea, or vomiting which progresses to pallor or cyanosis, lassitude, drowsiness, hyperventilation due to acidosis, and cardiovascular collapse. Caution should be exercised in interpreting serum iron levels in the 24 hours following the administration of Ferrlecit® since many laboratory assays will falsely overestimate serum or transferrin bound iron by measuring iron still bound to the Ferrlecit® complex. Additionally, in the assessment of iron overload, caution should be exercised in interpreting serum ferritin levels in the week following Ferrlecit® administration since, in clinical studies, serum ferritin exhibited a non-specific rise which persisted for five days.

The Ferrlecit® iron complex is not dialyzable.

Ferrlecit® at elemental iron doses of 125 mg/kg, 78.8 mg/kg, 62.5 mg/kg and 250 mg/kg caused deaths to mice, rats, rabbits, and dogs respectively. The major symptoms of acute toxicity were decreased activity, staggering, ataxia, increases in the respiratory rate, tremor, and convulsions.

DOSAGE AND ADMINISTRATION

The dosage of Ferrlecit® is expressed in terms of mg of elemental iron. Each 5 mL ampule contains 62.5 mg of elemental iron (12.5 mg/mL).

The recommended dosage of Ferrlecit® for the repletion treatment of iron deficiency in hemodialysis patients is 10 mL of Ferrlecit® (125 mg of elemental iron). Ferrlecit® may be diluted in 100 mL of 0.9% sodium chloride administered by intravenous infusion over 1 hour. Ferrlecit® may also be administered undiluted as a slow IV injection (at a rate of up to 12.5 mg/min). Most patients will require a minimum cumulative dose of 1.0 gram of elemental iron, administered over eight sessions at sequential dialysis treatments, to achieve a favorable hemoglobin or hematocrit response. Patients may continue to require therapy with intravenous iron at the lowest dose necessary to maintain target levels of hemoglobin, hematocrit, and laboratory parameters of iron storage within acceptable limits. Ferrlecit® has been administered at sequential dialysis sessions by infusion or by slow IV injection during the dialysis session itself.

Pediatric Dosage: The recommended pediatric dosage of Ferrlecit® for the repletion treatment of iron deficiency in hemodialysis patients is 0.12 mL/kg Ferrlecit® (1.5 mg/kg of elemental iron) diluted in 25 mL 0.9% sodium chloride and administered by intravenous infusion over 1 hour at eight sequential dialysis sessions. The maximum dosage should not exceed 125 mg per dose.

Note: Do not mix Ferrlecit® with other medications, or add to parenteral nutrition solutions for intravenous infusion. The compatibility of Ferrlecit® with intravenous infusion vehicles other than 0.9% sodium chloride has not been evaluated. Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever the solution and container permit.

If diluted in saline, use immediately after dilution.

HOW SUPPLIED

NDC 52544-922-26

Ferrlecit® is supplied in colorless glass ampules. Each ampule contains 62.5 mg of elemental iron in 5 mL for intravenous use, packaged in cartons of 10 ampules.

Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F). Do not freeze. See USP Controlled Room Temperature.

Keep out of the reach of children.

Rx Only

February 2004.

WATSON Pharma, Inc.

A Subsidiary of Watson Pharmaceuticals, Inc.

Venofer®
(iron sucrose injection, USP)

Rx Only

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DESCRIPTION

Venofer® (iron sucrose injection, USP) is a brown, sterile, aqueous, complex of polynuclear iron (III)-hydroxide in sucrose for intravenous use. Iron sucrose injection has a molecular weight of approximately 34,000 - 60,000 daltons and a proposed structural formula:

$$[Na_2Fe_5O_8(OH) \cdot 3(H_2O)]_n \cdot m(C_{12}H_{22}O_{11})$$

where: n is the degree of iron polymerization and m is the number of sucrose molecules associated with the iron (III)-hydroxide.

Each mL contains 20 mg elemental iron as iron sucrose in water for injection. Venofer® is available in 5 mL single dose vials (100 mg elemental iron per 5 mL). The drug product contains approximately 30% sucrose w/v (300 mg/mL) and has a pH of 10.5-11.1. The product contains no preservatives. The osmolarity of the injection is 1,250 mOsmol/L.

Therapeutic class: Hematinic

CLINICAL PHARMACOLOGY

Pharmacodynamics: Following intravenous administration of Venofer®, iron sucrose is dissociated by the reticuloendothelial system into iron and sucrose. In 22 hemodialysis patients on erythropoietin (recombinant human erythropoietin) therapy treated with iron sucrose containing 100 mg of iron, three times weekly for three weeks, significant increases in serum iron and serum ferritin and significant decreases in total iron binding capacity occurred four weeks from the initiation of iron sucrose treatment.

Pharmacokinetics: In healthy adults treated with intravenous doses of Venofer®, its iron component exhibits first order kinetics with an elimination half-life of 6 h, total clearance of 1.2 L/h, non-steady state apparent volume of distribution of 10.0 L and steady state apparent volume of distribution of 7.9 L. Since iron disappearance from serum depends on the need for iron in the iron stores and iron utilizing tissues of the body, serum clearance of iron is expected to be more rapid in iron deficient patients treated with Venofer® as compared to healthy individuals. The effects of age and gender on the pharmacokinetics of Venofer® have not been studied.

Venofer® is not dialyzable through CA210 (Baxter) High Efficiency or Fresenius F80A High Flux dialysis membranes. In *in vitro* studies, the amount of iron sucrose in the dialysate fluid was below the levels of detection of the assay (less than 2 parts per million).

Distribution: In healthy adults receiving intravenous doses of Venofer®, its iron component appears to distribute mainly in blood and to some extent in extravascular fluid. A study evaluating Venofer® containing 100 mg of iron labeled with $^{52}Fe/^{59}Fe$ in patients with iron deficiency shows that a significant amount of the administered iron distributes in the liver, spleen and bone marrow and that the bone marrow is an iron trapping compartment and not a reversible volume of distribution.

Metabolism and Elimination: Following intravenous administration of Venofer®, iron sucrose is dissociated into iron and sucrose by the reticuloendothelial system. The sucrose component is eliminated mainly by urinary excretion. In a study evaluating a single intravenous dose of Venofer® containing 1,510 mg of sucrose and 100 mg of iron in 12 healthy adults (9 female, 3 male: age range 32-52), 68.3% of the sucrose was eliminated in urine in 4 h and 75.4% in 24 h. Some iron also is eliminated in the urine. Neither transferrin nor transferrin receptor levels changed immediately after the dose administration [1]. In this study and another study evaluating a single intravenous dose of iron sucrose containing 500-700 mg of iron in 26 anemic patients on erythropoietin therapy (23 female, 3 male; age range 16-60), approximately 5% of the iron was eliminated in urine in 24 h at each dose level [2].

Drug-drug interactions: Drug-drug interactions involving Venofer® have not been studied. However, like other parenteral iron preparations, Venofer® may be expected to reduce the absorption of concomitantly administered oral iron preparations.

CLINICAL TRIALS

Venofer® is used to replenish body iron stores in patients with iron deficiency on chronic hemodialysis and receiving erythropoietin. In these patients iron deficiency is caused by blood loss during dialysis procedure, increased erythropoiesis, and insufficient absorption of iron from the gastrointestinal tract. Iron is essential to the synthesis of hemoglobin to maintain oxygen transport and to the function and formation of other physiologically important heme and nonheme compounds. Most hemodialysis patients require intravenous iron to maintain sufficient iron stores to achieve and maintain a hemoglobin of 11-12 g/dL.

Three clinical trials were conducted to assess the safety and efficacy of Venofer®. Two studies were conducted in United States (100 patients) and one was conducted in South Africa (131 patients).

Study A

Study A was a multicenter, open-label, historically-controlled study in 101 hemodialysis patients (77 patients with Venofer® treatment and 24 in the historical control group) with iron deficiency anemia. Eligibility for Venofer® treatment included patients undergoing chronic hemodialysis three times weekly, receiving erythropoietin, hemoglobin concentration greater than 8.0 and less than 11.0 g/dL for at least two consecutive weeks, transferrin saturation < 20%, and serum ferritin < 300 ng/mL. The mean age of the patients in the treatment group was 65 years with the age range being 31 to 85 years of age. The erythropoietin dose was to be held constant throughout the study. The protocol did not require administration of a test dose; however, some patients received a test dose at the physician's discretion. Exclusion criteria included significant underlying disease, asthma, active inflammatory disease, or serious bacterial or viral infection. Venofer® 5 mL (one vial) containing 100 mg of elemental iron was administered through the dialysis line at each dialysis session either as slow injection or a saline diluted slow infusion for a total of 10 dialysis sessions with a cumulative dose of 1000 mg elemental iron. A maximum of 3 vials of Venofer® was administered per week. No additional iron preparations were allowed until after the Day 57 evaluation. The mean change in hemoglobin from baseline to Day 24 (end of treatment), Day 36, and Day 57 was assessed.

The historical control population consisted of 24 patients with similar ferritin levels as patients treated with Venofer®, who were off intravenous iron for at least 2 weeks and who had received erythropoietin therapy with hematocrit averaging 31-36 for at least two months prior to study entry. The mean age of patients in the historical control group was 56 years, with an age range of 29 to 80 years. Patient age and serum ferritin levels were similar between treatment and historical control patients. Of the 77 patients in the treatment group, 44 (57%) were male and 33 (43%) were female. The mean baseline hemoglobin, hematocrit, were higher and erythropoietin dose was lower in the historical control population than the Venofer® treated population.

Patients in the Venofer® treated population showed a statistically significantly greater increase in hemoglobin and hematocrit than did patients in the historical control population. See Table 1.

Table 1. Changes from Baseline in Hemoglobin and Hematocrit

Efficacy parameters	End of treatment		2 week follow-up		5 week follow-up	
	Venofer® (n=69)	Historical Control (n=18)	Venofer® (n=73)	Historical Control (n=18)	Venofer® (n=71)	Historical Control (n=15)
Hemoglobin (g/dL)	1.0±0.12**	0.0±0.21	1.3±0.14**	-0.6±0.24	1.2±0.17*	-0.1±0.23
Hematocrit (%)	3.1±0.37**	-0.3±0.65	3.6±0.44**	-1.2±0.76	3.3±0.54	0.2±0.86

**p<0.01 and *p<0.05 compared to historical control from ANCOVA analysis with baseline hemoglobin, serum ferritin and erythropoietin dose as covariates.

Serum ferritin increased significantly (p=0.0001) at endpoint of study from baseline in the Venofer®-treated population (165.3±24.2 ng/mL) compared to the historical control population (-27.6±9.5 ng/mL). Transferrin saturation also increased significantly (p=0.0018) at endpoint of study from baseline in the Venofer®-treated population (8.8±1.6%) compared to this historical control population (-5.1±4.3%) [3].

Study B

Study B was a multicenter, open label study of Venofer® (iron sucrose injection, USP) in 23 iron deficient hemodialysis patients who had been discontinued from iron dextran due to intolerance. Eligibility criteria and Venofer® administration were otherwise identical to Study A. The mean age of the patients in this study was 53 years, with ages ranging from 21-79 years. Of the 23 patients enrolled in the study, 10 (44%) were male and 13 (56%) were female. The ethnicity breakdown of patients enrolled in this study was as follows: Caucasian - 8 (35%); Black - 8 (35%); Asian - 1 (4%); Hispanic - 6 (26%). The mean change from baseline to the end of treatment (Day 24) in hemoglobin, hematocrit, and serum iron parameters was assessed.

All 23 enrolled patients were evaluated for efficacy. Statistically significant increases in mean hemoglobin (1.1±0.2 g/dL), hematocrit (3.6±0.6%), serum ferritin (266.3±30.3 ng/mL) and transferrin saturation (8.7±2.0%) were observed from baseline to end of treatment [4].

Study C

Study C was a multicenter, open-label, two period (treatment followed by observation period) study in iron deficient hemodialysis patients. Eligibility for this study included chronic hemodialysis patients with a hemoglobin less than or equal to 10 g/dL, a serum transferrin saturation less than or equal to 20%, and a serum ferritin less than or equal to 200 ng/mL, who were undergoing maintenance hemodialysis 2 to 3 times weekly. The mean age of the patients enrolled in this study was 41 years, with ages ranging from 16-70 years. Of 130 patients evaluated for efficacy in this study, 68 (52%) were male and 62 (48%) were female. The ethnicity breakdown of patients enrolled in this study was as follows: Caucasian - 30 (23%); Black - 30 (23%); Asian - 6 (5%); Other (mixed ethnicity) - 64 (49%). Forty-eight percent of the patients had previously been treated with oral iron. Exclusion criteria were similar to those in studies A and B. Venofer®, was administered in doses of 100 mg during sequential dialysis sessions until a pre-determined (calculated) total dose of iron was administered.

Patients received Venofer® at each dialysis session, two to three times weekly. One hour after the start of each session, 5 mL iron sucrose (100 mg iron) in 100 mL 0.9% NaCl was administered into the hemodialysis line. A 50 mg dose (2.5 mL) was given to patients within two weeks of study entry. Patients were treated until they reached an individually calculated total iron dose based on baseline hemoglobin level and body weight. Twenty-seven patients (20%) were receiving erythropoietin treatment at study entry and they continued to receive the same erythropoietin dose for the duration of the study.

Changes from baseline to observation week 2 and observation week 4 (end of study) were analyzed.

The modified intention-to-treat population consisted of 131 patients. Significant (p<0.0001) increases from baseline in mean hemoglobin (1.7 g/dL), hematocrit (5%), serum ferritin (434.6 ng/mL), and serum transferrin saturation (14%) were observed at week 2 of the observation period and these values remained significantly increased (p<0.0001) at week 4 of the observation period.

CLINICAL INDICATIONS AND USAGE

Venofer® is indicated in the treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy.

CONTRAINDICATIONS

The use of Venofer® is contraindicated in patients with evidence of iron overload, in patients with known hypersensitivity to Venofer® or any of its inactive components, and in patients with anemia not caused by iron deficiency.

WARNINGS

Hypersensitivity reactions have been reported with injectable iron products. See **PRECAUTIONS** and **ADVERSE REACTIONS**.

PRECAUTIONS

General:

Because body iron excretion is limited and excess tissue iron can be hazardous, caution should be exercised to withhold iron administration in the presence of evidence of tissue iron overload. Patients receiving Venofer® require periodic monitoring of hematologic and hematinic parameters (hemoglobin, hematocrit, serum ferritin and transferrin saturation). Iron therapy should be withheld in patients with evidence of iron overload. Transferrin saturation values increase rapidly after IV administration of iron sucrose; thus, serum iron values may be reliably obtained 48 hours after IV dosing. (See **DOSAGE AND ADMINISTRATION** and **OVERDOSAGE**).

Hypersensitivity Reactions:

Serious hypersensitivity reactions have been rarely reported in patients receiving Venofer®. No life-threatening hypersensitivity reactions were observed in Studies A, B, and C, and two post-marketing safety studies. Several cases of mild or moderate hypersensitivity reactions were observed in these studies. A total of 83 anaphylactoid reactions including serious or life-threatening reactions have been reported in post-marketing spontaneous reports worldwide between 1992 and 2002 based on estimated use in more than 2 million patients. See **ADVERSE REACTIONS**.

Hypotension:

Hypotension has been reported frequently in hemodialysis patients receiving intravenous iron. Hypotension following administration of Venofer® may be related to rate of administration and total dose administered. Caution should be taken to administer Venofer® according to recommended guidelines. See **DOSAGE AND ADMINISTRATION**.

Venofer®
(iron sucrose injection, USP)

Rx Only

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Drug Interactions:

Venofer® (iron sucrose injection, USP) should not be administered concomitantly with oral iron preparations since the absorption of oral iron is reduced.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

No long-term studies in animals have been performed to evaluate the carcinogenic potential of Venofer®.

Venofer® was not genotoxic in the Ames test, the mouse lymphoma cell (L5178Y/TK+/-) forward mutation test, the human lymphocyte chromosome aberration test, or the mouse micronucleus test.

Venofer® at IV doses up to 15 mg iron/kg/day (about 1.2 times the recommended maximum human dose on a body surface area basis) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy Category B:

Teratology studies have been performed in rats at IV doses up to 13 mg iron/kg/day (about 0.5 times the recommended maximum human dose on a body surface area basis) and rabbits at IV doses up to 13 mg iron/kg/day (about 1 times the recommended maximum human dose on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to Venofer®. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers:

Venofer® is excreted in milk of rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Venofer® is administered to a nursing woman.

Pediatric Use:

Safety and effectiveness of Venofer® in pediatric patients have not been established. In a country where Venofer® is available for use in children, at a single site, five premature infants (weight less than 1,250 g) developed necrotizing enterocolitis and two of the five expired during or following a period when they received Venofer®, several other medications and erythropoietin. Necrotizing enterocolitis may be a complication of prematurity in very low birth weight infants. No causal relationship to Venofer® or any other drugs could be established.

Geriatric Use:

Studies A, B, and C did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. Of the 1,051 patients in two post-marketing safety studies of Venofer®, 40% were 65 years and older. No overall differences in safety were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Exposure to Venofer® has been documented in 231 patients undergoing chronic hemodialysis in the above mentioned clinical trials and in 1,051 patients undergoing hemodialysis in two post-marketing safety studies. About 1,600 hemodialysis patients treated with Venofer® have been reported in the medical literature.

The safety of Venofer® has been documented in three efficacy studies (A, B, and C previously described) and two post-marketing studies involving a total of 1,282 patients.

In the first post-marketing safety study, 665 chronic hemodialysis patients were treated with Venofer® doses of 100 mg at each dialysis session for up to 10 consecutive dialysis sessions for their iron deficiency or on a weekly basis for 10 weeks for maintenance of iron stores. Serious adverse events and drug-related non-serious adverse events were collected. In the second post-marketing safety study, 386 hemodialysis patients were exposed to a single dose of Venofer® (100 mg IV by slow injection over 2 minutes or 200 mg IV by slow injection over 5 minutes). The mean age of patients enrolled into the two post-marketing safety studies was 59 years, with a range of 20-93 years. Males made up 60% of the population. The ethnicity of the patients enrolled in the two studies included Blacks (44%), Caucasians (41%), Asians (3%), Hispanics (11%) and others (1%).

Adverse Events Observed in Studies A, B, and C:

Adverse reactions, whether or not related to Venofer® administration, reported by >5% of treated patients from a total of 231 patients in the three studies are as follows: hypotension (36%), cramps/leg cramps (23%), nausea, headache, vomiting, and diarrhea.

Adverse events, whether or not related to Venofer® administration, reported by >1% of treated patients from a total of 231 patients in the three studies are categorized below by body system either by investigator term or by COSTART terminology and ranked in order of decreasing frequency within each body system. Some of these symptoms may be seen in patients with chronic renal failure or on hemodialysis not receiving intravenous iron.

Body as a Whole: headache, fever, pain, asthenia, unwell, malaise, accidental injury.

Cardiovascular Disorders, General: hypotension, chest pain, hypertension, hypervolemia.

Gastrointestinal System Disorders: nausea, vomiting, abdominal pain, elevated liver enzymes.

Central and Peripheral Nervous System: dizziness.

Musculoskeletal System: cramps/leg cramps, musculoskeletal pain.

Respiratory System: dyspnea, pneumonia, cough.

Skin and appendages: pruritus, application site reaction.

Adverse Events Observed in Two Post-Marketing Safety Studies:

In the two post-marketing safety studies, 665 patients received multiple doses of Venofer®, and 386 patients received a single dose of Venofer®. In the multiple dose study, 72% of the patients received up to 10 doses, 27% received between 11-30 doses and 1% received 40 to 50 doses of Venofer®; only serious adverse events and non-serious adverse events considered by the investigators to be drug related were collected.

Adverse events reported by >1% of 1,051 treated patients are as follows: congestive heart failure, sepsis and taste perversion.

Hypersensitivity Reactions: See **WARNINGS** and **PRECAUTIONS**.

In Studies A, B, and C, and two post-marketing safety studies, several patients experienced mild or moderate hypersensitivity reactions presenting with wheezing, dyspnea, hypotension, rashes, or pruritus.

No serious or life-threatening hypersensitivity reactions associated with Venofer® administration were observed in these studies. From the post-marketing spontaneous reporting system, there were 83 reports of anaphylactoid reactions including patients who experienced serious or life-threatening reactions (anaphylactic shock, loss of consciousness or collapse, bronchospasm with dyspnea, or convulsion) associated with Venofer® administration between 1992 and 2002 based on estimated use in more than 2 million patients.

One hundred thirty (11%) of the 1,151 patients evaluated in the 4 U.S. trials had prior other intravenous iron therapy and were reported to be intolerant (defined as precluding further use of that iron product). When these patients were treated with Venofer® there were no occurrences of adverse events that precluded further use of Venofer®.

OVERDOSAGE

Dosages of Venofer® (iron sucrose injection, USP) in excess of iron needs may lead to accumulation of iron in storage sites leading to hemosiderosis. Periodic monitoring of iron parameters such as serum ferritin and transferrin saturation may assist in recognizing iron accumulation. Venofer® should not be administered to patients with iron overload and should be discontinued when serum ferritin levels equal or exceed established guidelines [5]. Particular caution should be exercised to avoid iron overload where anemia unresponsive to treatment has been incorrectly diagnosed as iron deficiency anemia.

Symptoms associated with overdosage or infusing Venofer® too rapidly included hypotension, headache, vomiting, nausea, dizziness, joint aches, paresthesia, abdominal and muscle pain, edema, and cardiovascular collapse. Most symptoms have been successfully treated with IV fluids, hydrocortisone, and/or antihistamines. Infusing the solution as recommended or at a slower rate may also alleviate symptoms.

Preclinical Data:

Single IV doses of Venofer® at 150 mg iron/kg in mice (about 3 times the recommended maximum human dose on a body surface area basis) and 100 mg iron/kg in rats (about 8 times the recommended maximum human dose on a body surface area basis) were lethal.

The symptoms of acute toxicity were sedation, hypoactivity, pale eyes, and bleeding in the gastrointestinal tract and lungs.

DOSAGE AND ADMINISTRATION

The dosage of Venofer® is expressed in terms of mg of elemental iron. Each mL contains 20 mg of elemental iron.

The recommended dosage of Venofer® for the repletion treatment of iron deficiency in hemodialysis patients is 5 mL of Venofer® (100 mg of elemental iron) delivered intravenously during the dialysis session. Most patients will require a minimum cumulative dose of 1,000 mg of elemental iron, administered over 10 sequential dialysis sessions, to achieve a favorable hemoglobin or hematocrit response. Patients may continue to require therapy with Venofer® or other intravenous iron preparations at the lowest dose necessary to maintain target levels of hemoglobin, hematocrit and laboratory parameters of iron storage within acceptable limits.

Administration: Venofer® must only be administered intravenously either by slow injection or by infusion. In clinical trials, Venofer® was administered intravenously directly into the dialysis line.

Slow Intravenous Injection: In chronic renal failure patients, Venofer® may be administered undiluted by slow intravenous injection into the dialysis line at a rate of 1 mL (20 mg iron) solution per minute [i.e., 5 minutes per vial] not exceeding one vial Venofer® (100 mg iron) per injection. Discard any unused portion.

Infusion: Venofer® may also be administered by infusion (into the dialysis line for hemodialysis patients). The content of each vial must be diluted exclusively in a maximum of 100 mL of 0.9% NaCl, immediately prior to infusion. The solution should be infused at a rate of 100 mg of iron over a period of at least 15 minutes. Unused diluted solution should be discarded.

NOTE: Do not mix Venofer® with other medications or add to parenteral nutrition solutions for intravenous infusion. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever the solution and container permit.

Recommended Dosage:

Adults: 100 mg iron administered one to three times per week to a total dose of 1,000 mg in 10 doses, repeat if needed. Frequency of dosing should be no more than three times weekly. Patients may continue to require therapy with intravenous iron at the lowest dose necessary to maintain levels of hemoglobin, hematocrit, and laboratory parameters of iron storage within acceptable limits.

HOW SUPPLIED

Venofer® is supplied in 5 mL single dose vials. Each 5 mL vial contains 100 mg elemental iron (20 mg/mL). Contains no preservatives. Store in original carton at 25°C (77°F). Excursions permitted to 15°-30°C (59°-86°F). [See the USP controlled room temperature]. Do not freeze.

Sterile

NDC-0517-2340-01	100 mg/5 mL Single Dose Vial	Individually Boxed
NDC-0517-2340-10	100 mg/5 mL Single Dose Vial	Packages of 10

Rx Only

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