CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-135

FINAL PRINTED LABELING

LABELING

Venofer® (iron sucrose injection)

DESCRIPTION

Venofer® (iron sucrose injection) 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.

Venofer® is available in 5 mL single dose vials. Each 5 mL contains 100 mg (20 mg/mL) of elemental iron as iron sucrose in water for injection. 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 1250 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.

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 52Fe/59Fe 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 1510 mg of sucrose and 100 mg of iron in 12 healthy adults, 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. 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, approximately 5% of the iron was eliminated in urine in 24 h at each dose level.

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 and one was conducted in South Africa.

Study A

Study A was a multicenter, open-label, historically-controlled study in 101 hemodialysis patients (77 patients with Venofer® treatment and 24 in historical control) 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 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 level 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.

Patient age and serum ferritin level were similar between treatment and historical control patients. The mean baseline hemoglobin, hematocrit, and erythropoietin dose were 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 EPO 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=0.0016) at endpoint of study from baseline in the Venofer®-treated population (8.8±1.6%) compared to the historical control population (-5.1±4.3%).

Study B

Study B was a multicenter, open label study of Venofer® 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 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.

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. 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 130 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:

POTENTIALLY FATAL HYPERSENSITIVITY REACTIONS CHARACTERIZED BY ANAPHYLACTIC SHOCK, LOSS OF CONSCIOUSNESS, COLLAPSE, HYPOTENSION, DYSPNEA, OR CONVULSION HAVE BEEN REPORTED RARELY IN PATIENTS RECEIVING VENOFER®(SEE ADVERSE REACTIONS). FATAL IMMEDIATE HYPERSENSITIVITY REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH MANY IRON CARBOHYDRATE COMPLEXES. FACILITIES FOR CARDIOPULMONARY RESUSCITATION MUST BE AVAILABLE DURING DOSING. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE APPROPRIATE RESUSCITATION MEASURES. ALTHOUGH FATAL HYPERSENSITIVITY REACTIONS HAVE NOT BEEN OBSERVED IN VENOFER® CLINICAL STUDIES, INSUFFICIENT NUMBERS OF PATIENTS MAY HAVE BEEN ENROLLED TO OBSERVE THIS EVENT. PHYSICIAN VIGILANCE WHEN ADMINISTERING ANY INTRAVENOUS IRON PRODUCT IS ADVISED (SEE PRECAUTIONS and ADVERSE REACTIONS).

HYPOTENSION:

HYPOTENSION HAS BEEN REPORTED FREQUENTLY IN 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).

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).

Drug Interactions:

Venofer® 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 i.v. 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 i.v. 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 i.v. 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 1250g) 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:

Clinical studies of Venofer® 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 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 Venofer® has been documented in 1004 patients with chronic renal failure. Of these, 231 were dialysis patients in the above mentioned clinical trials, and 773 were patients described in the medical literature.

The safety of Venofer® has been documented in 231 chronic renal failure patients exposed to single doses of 100 mg iron IV as iron sucrose given up to three times weekly for up to ten doses in 3 clinical trials. Of these, 100 were US (Studies A and B) and 131 were non-US patients (Study C). Adverse events were recorded by the investigator using terminology of their own choosing.

Common adverse events observed in 3 clinical trials:
Adverse events, whether or not related to Venofer® administration, reported by > 5% of treated patients from a total of 231 patients in three studies are as follows: hypotension (36%), cramps/leg cramps (23%), nausea, headache, vomiting, and diarrhea.

Adverse Events Observed During 3 Clinical Trials: Adverse events, whether or not related to Venofer® administration, reported by >1% of treated patients from a total of 231 patients in 3 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.

Hypersensitivity reactions: See WARNINGS.

In three clinical trials (231 patients) several patients experienced pruritis and one patient experienced a facial rash. No patients experienced generalized rashes or urticaria. No serious or life-threatening anaphylactoid reaction was observed in three trials and none of these reactions led to treatment discontinuation. From the spontaneous reporting system, 27 patients reported anaphylactoid reactions including 8 patients who experienced serious or life-threatening reactions (anaphylactic shock, loss of consciousness, collapse, hypotension, dyspnea, or convulsion) associated with Venofer® administration in the estimated more than 450,000 patients exposed to Venofer® between 1992 and 1999.

OVERDOSAGE

Dosages of Venofer® 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 [1]. 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 i.v. 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 5 mL vial contains 100 mg of elemental iron (20 mg/mL).

Of the three clinical studies in hemodialysis patients, the two U.S. studies (100 patients) did not require a test dose; however, some patients received a test dose at the physician's discretion. In a non-U.S. study, 131 patients received a first dose of Venofer® [2.5mL (50mg elemental iron) diluted in 50mL 0.9% NaCl] administered over 3 to 10 minutes.

The recommended dosage of Venofer for the repletion treatment of iron deficiency in hemodialysis patients is 5mL of Venofer® (100 mg of elemental iron) delivered intravenously during the dialysis session. Most patients will require a minimum cumulative dose of 1000 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 (directly into the dialysis line) either by slow injection or by infusion.

Slow Intravenous injection: In chronic renal failure patients, Venofer® may be administered by slow intravenous injection into the dialysis line at a rate of 1 mL (20 mg iron) undiluted 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). This may reduce the risk of hypotensive episodes. 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: 100mg iron administered one to three times per week to a total dose of 1000 mg in 10 doses, repeat if needed. Frequency of dosing should be no more than three times weekly.

HOW SUPPLIED

Venofer® is supplied in 5 mL single dose vials. Each 5mL vial contains 100 mg elemental iron (20 mg/mL). Contains r preservatives. Packaged in cartons containing 10 single dose vials. 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

Venofer is a registered trademark of Vifor International, Inc.

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CAUTION: Rx ONLY

[1] NKF-DOQI Clinical Practice Guidelines for the Treatment of Anemia of Chronic Renal Failure, New York Kidney Foundation, 1997.