HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Venofer safely and effectively. See full prescribing information for Venofer.

***Venofer*® (iron sucrose injection, USP)**

Initial U.S. Approval: 2000

----------RECENT MAJOR CHANGES----------

- Warnings and Precautions (5.1) 6/2011

----------INDICATIONS AND USAGE----------

Venofer is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease (CKD). (1)

----------DOSAGE AND ADMINISTRATION----------

Administer Venofer intravenously either by slow injection or by infusion. (2.1)

- CKD patients on hemodialysis: 100 mg undiluted slow intravenous injection over 2 to 5 minutes or as an infusion of 100 mg, diluted in a maximum of 100 mL of 0.9% NaCl, over a period of at least 15 minutes. (2.2)
- CKD patients not on dialysis: 200 mg undiluted slow intravenous injection over 2 to 5 minutes.
- CKD patients receiving peritoneal dialysis: infuse 300 mg over 1.5 hours given on two occasions 14 days apart followed by a single infusion 14 days later of 400 mg given over 2.5 hours. Dilute each Venofer dose in a maximum volume of 250 mL of 0.9% NaCl. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

- 10 mL single use vial / 200 mg elemental iron (20 mg/mL) (3)
- 5 mL single use vial / 100 mg elemental iron (20 mg/mL) (3)
- 2.5 mL single use vial / 50 mg elemental iron (20 mg/mL) (3)

---------- CONTRAINDICATIONS----------

- Known hypersensitivity to Venofer (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity Reactions: Observe for signs and symptoms of hypersensitivity during and after Venofer administration for at least 30 minutes and until clinically stable following completion of each administration. Only administer Venofer when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions. (5.1)
- Hypotension: Venofer may cause hypotension. Monitor for signs and symptoms of hypotension during and following each administration of Venofer. (5.2)
- Iron Overload: Regularly monitor hematologic responses during Venofer therapy. Do not administer Venofer to patients with iron overload. (5.3)

----------ADVERSE REACTIONS----------

- The most common adverse reactions (≥2%) following the administration of Venofer are diarrhea, nausea, vomiting, headache, dizziness, hypotension, pruritus, pain in extremity, arthralgia, back pain, muscle cramp, injection site reactions, chest pain, and peripheral edema (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact American Regent, Inc. at 1-800-734-9236 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 6/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Venofer is indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease.

2 DOSAGE AND ADMINISTRATION

Venofer must only be administered intravenously either by slow injection or by infusion. The dosage of Venofer is expressed in terms of mg of elemental iron. Each mL contains 20 mg of elemental iron. The usual total treatment course of Venofer is 1000 mg**.** Venofer treatment may be repeated if iron deficiency reoccurs.

2.1 Adult Patients with CKD on dialysis

Administer Venofer 100 mg undiluted as a slow intravenous injection over 2 to 5 minutes, or as an infusion of 100 mg diluted in a maximum of 100 mL of 0.9% NaCl over a period of at least 15 minutes, per consecutive hemodialysis session. Venofer should be administered early during the dialysis session.

2.2 Adult Patients with CKD not on dialysis

Administer Venofer 200 mg undiluted as a slow intravenous injection over 2 to 5 minutes on 5 different occasions over a 14 day period. There is limited experience with administration of an infusion of 500 mg of Venofer, diluted in a maximum of 250 mL of 0.9% NaCl, over a period of 3.5 to 4 hours on day 1 and day 14.

2.3 Adult Patients with CKD receiving peritoneal dialysis

Administer Venofer in 3 divided doses, given by slow intravenous infusion, within a 28 day period: 2 infusions each of 300 mg over 1.5 hours 14 days apart followed by one 400 mg infusion over 2.5 hours 14 days later. Dilute Venofer in a maximum of 250 mL of 0.9% NaCl.

3 DOSAGE FORMS AND STRENGTHS

- 10 mL single use vial / 200 mg elemental iron (20 mg/mL)
- 5 mL single use vial / 100 mg elemental iron (20 mg/mL)
- 2.5 mL single use vial / 50 mg elemental iron (20 mg/mL)

4 CONTRAINDICATIONS

Venofer is contraindicated in patients with:

- Known hypersensitivity to Venofer

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving Venofer. Patients may present with shock, clinically significant hypotension, loss of consciousness, and/or collapse. If hypersensitivity reactions or signs of intolerance occur during administration, stop Venofer immediately. Monitor patients for signs and symptoms of hypersensitivity during and after Venofer administration for at least 30 minutes and until clinically stable following completion of the infusion. Only administer Venofer when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions. Most reactions associated with intravenous iron preparations occur within 30 minutes of the completion of the infusion *[see Adverse Reactions from Post-marketing Spontaneous Reports (6.1 and 6.2)]*.

5.2 Hypotension

Venofer may cause clinically significant hypotension. Monitor for signs and symptoms of hypotension following each administration of Venofer. Hypotension following administration of Venofer may be related to the rate of administration and/or total dose administered *[See Dosage and Administration (2), Warnings and Precautions (5.1), and Adverse Reactions from Post-marketing Spontaneous Reports (6.2)]*.

5.3 Iron Overload

Excessive therapy with parenteral iron can lead to excess storage of iron with the possibility of iatrogenic hemosiderosis. Patients receiving Venofer require periodic monitoring of hematologic and iron parameters (hemoglobin, hematocrit, serum ferritin and transferrin saturation). Do not administer Venofer to patients with evidence of iron overload. Transferrin saturation values increase rapidly after intravenous administration of iron sucrose; do not perform serum iron measurements for at least 48 hours after intravenous dosing. *[See Dosage and Administration (2) and Overdosage (10)]*

6 ADVERSE REACTIONS

Venofer injection may cause serious hypersensitivity reactions and hypotension. *[See Warnings and Precautions (5.1; 5.2)]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug may not reflect the rates observed in practice.

6.1 Adverse Reactions in Clinical Studies

The frequency of adverse reactions associated with the use of Venofer has been documented in six clinical trials involving 231 patients with HDD-CKD, 139 patients with NDD-CKD and 75 patients with PDD-CKD. Treatment-emergent adverse events reported by ≥ 2% of treated patients in the six clinical trials for which the rate for Venofer exceeds the rate for comparator are listed by indication in Table 1. Patients with HDD-CKD received 100 mg doses at 10 consecutive dialysis sessions until a cumulative dose of 1000 mg was administered. Patients with NDD-CKD received either 5 doses of 200 mg over 2 weeks or 2 doses of 500 mg separated by fourteen days, and patients with PDD-CKD received 2 doses of 300 mg followed by a dose of 400 mg over a period of 4 weeks.

Table 1. Treatment-Emergent Adverse Reactions Reported in ≥ 2% of Study Populations and for which the Rate for Venofer Exceeds the Rate for Comparator

Adverse Reactions (Preferred Term)	HDD-CKD	NDD-CKD		PDD-CKD	
	Venofer (N=231) %	Venofer (N=139) %	Oral Iron (N=139) %	Venofer (N=75) %	EPO* Only (N=46) %
Subjects with any adverse reaction	78.8	76.3	73.4	72.0	65.2
Ear and Labyrinth Disorders					
Ear Pain	0	2.2	0.7	0	0
Eye Disorders					
Conjunctivitis	0.4	0	0	2.7	0
Gastrointestinal Disorders					
Abdominal pain	3.5	1.4	2.9	4.0	6.5
Diarrhea	5.2	7.2	10.1	8.0	4.3
Dysgeusia	0.9	7.9	0	0	0
Nausea	14.7	8.6	12.2	5.3	4.3
Vomiting	9.1	5.0	8.6	8.0	2.2
General Disorders and Administration Site Conditions					
Asthenia	2.2	0.7	2.2	2.7	0
Chest pain	6.1	1.4	0	2.7	0
Feeling abnormal	3.0	0	0	0	0
Infusion site pain or burning	0	5.8	0	0	0
Injection site extravasation	0	2.2	0	0	0
Peripheral edema	2.6	7.2	5.0	5.3	10.9
Pyrexia	3.0	0.7	0.7	1.3	0
Infections and Infestations					
Nasopharyngitis, Sinusitis, Upper respiratory tract infections, Pharyngitis	2.6	2.2	4.3	16.0	4.3
Injury, Poisoning and Procedural Complications					
Graft complication	9.5	1.4	0	0	0
Metabolism and Nutrition Disorders					
Fluid overload	3.0	1.4	0.7	1.3	0
Gout	0	2.9	1.4	0	0
Hyperglycemia	0	2.9	0	0	2.2
Hypoglycemia	0.4	0.7	0.7	4.0	0
Musculoskeletal and Connective Tissue Disorders					
Arthralgia	3.5	1.4	2.2	4.0	4.3

Adverse Reactions (Preferred Term)	HDD-CKD	NDD-CKD		PDD-CKD	
	Venofer (N=231) %	Venofer (N=139) %	Oral Iron (N=139) %	Venofer (N=75) %	EPO* Only (N=46) %
Back pain	2.2	2.2	3.6	1.3	4.3
Muscle cramp	29.4	0.7	0.7	2.7	0
Myalgia	0	3.6	0	1.3	0
Pain in extremity	5.6	4.3	0	2.7	6.5
Nervous System Disorders					
Dizziness	6.5	6.5	1.4	1.3	4.3
Headache	12.6	2.9	0.7	4.0	0
Respiratory, Thoracic and Mediastinal Disorders					
Cough	3.0	2.2	0.7	1.3	0
Dyspnea	3.5	5.8	1.4	1.3	2.2
Nasal congestion	0	1.4	2.2	1.3	0
Skin and Subcutaneous Tissue Disorders					
Pruritus	3.9	2.2	4.3	2.7	0
Vascular Disorders					
Hypertension	6.5	6.5	4.3	8.0	6.5
Hypotension	39.4	2.2	0.7	2.7	2.2

* EPO=Erythropoietin

One hundred thirty (11%) of the 1,151 patients evaluated in the 4 U.S. trials in HDD-CKD patients (studies A, B and the two post marketing studies) 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 reactions that precluded further use of Venofer. *[See Warning and Precautions (5)]*

6.2 Adverse Reactions from Post-Marketing Spontaneous Reports

In the post-marketing safety studies in 1,051 treated patients with HDD-CKD, the adverse reactions reported by > 1% were: cardiac failure congestive, sepsis and dysgeusia.

The following additional adverse reactions have been identified with the use of Venofer from postmarketing spontaneous reports: Anaphylactic-type reactions, shock, loss of consciousness, collapse, bronchospasm, dyspnea, convulsions, light-headedness, confusion, angioedema, swelling of the joints, hyperhidrosis, back pain, bradycardia, and chromaturia. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Symptoms associated with Venofer total dosage or infusing too rapidly included hypotension, dyspnea, headache, vomiting, nausea, dizziness, joint aches, paresthesia, abdominal and muscle pain, edema, and cardiovascular collapse. These adverse reactions have occurred up to 30 minutes after the administration of Venofer injection. Reactions have occurred following the first dose or subsequent doses of Venofer. Symptoms may respond to IV fluids, hydrocortisone, and/or antihistamines. Slowing the infusion rate may alleviate symptoms.

7 DRUG INTERACTIONS

Drug interactions involving Venofer have not been studied. However, Venofer may reduce the absorption of concomitantly administered oral iron preparations.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. In animal reproduction studies, iron sucrose was administered intravenously to rats and rabbits during the period of organogenesis at doses up to 13 mg/kg/day of elemental iron (half or equivalent to the maximum recommended human dose based on body surface area, respectively) and revealed no evidence of harm to the fetus due to iron sucrose. Because animal reproductive studies are not always predictive of human response, Venofer should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether iron sucrose is excreted in human milk. Iron sucrose is secreted into the milk of lactating rats. Because many drugs are excreted in human milk, caution should be exercised when Venofer is administered to a nursing woman.

8.4 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 died 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.

8.5 Geriatric Use

Clinical **s**tudies of Venofer 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. In general, dose administration to an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

No data are available regarding overdosage of Venofer in humans. Excessive dosages of Venofer may lead to accumulation of iron in storage sites potentially leading to hemosiderosis. Do not administer Venofer to patients with iron overload. *[See Contraindications (4)]*

Toxicities in single-dose studies in mice and rats, at intravenous iron sucrose doses up to 8 times the maximum recommended human dose based on body surface area, included sedation, hypoactivity, pale

eyes, bleeding in the gastrointestinal tract and lungs, and mortality.

11 DESCRIPTION

Venofer (iron sucrose injection, USP), an iron replacement product, 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 to 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 10 mL single use vials (200 mg elemental iron per 10 mL), 5 mL single use vials (100 mg elemental iron per 5 mL), and 2.5 mL single use vials (50 mg elemental iron per 2.5 mL). The drug product contains approximately 30% sucrose w/v (300 mg/mL) and has a pH of 10.5 to 11.1. The product contains no preservatives. The osmolarity of the injection is 1,250 mOsmol/L.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Venofer is an aqueous complex of poly-nuclear iron (III)-hydroxide in sucrose. Following intravenous administration, Venofer is dissociated into iron and sucrose and the iron is transported as a complex with transferrin to target cells including erythroid precursor cells. The iron in the precursor cells is incorporated into hemoglobin as the cells mature into red blood cells.

12.2 Pharmacodynamics

Following intravenous administration, Venofer is dissociated into iron and sucrose. In 22 patients undergoing hemodialysis and receiving 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.

12.3 Pharmacokinetics

In healthy adults administered intravenous doses of Venofer, its iron component exhibited first order kinetics with an elimination half-life of 6 h, total clearance of 1.2 L/h, and steady state apparent volume of distribution of 7.9 L. The iron component appeared 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 showed that a significant amount of the administered iron distributed to the liver, spleen and bone marrow and that the bone marrow is an irreversible iron trapping compartment.

Following intravenous administration of Venofer, iron sucrose is dissociated into iron and sucrose. 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 to 52), 68.3% of the sucrose was eliminated in urine in 4 h and 75.4% in 24 h. Some iron was also eliminated in the urine. Neither transferrin nor transferrin receptor levels changed immediately after the dose administration. In this study and another study evaluating a single intravenous

dose of iron sucrose containing 500 to 700 mg of iron in 26 patients with anemia on erythropoietin therapy (23 female, 3 male; age range 16 to 60), approximately 5% of the iron was eliminated in urine in 24 h at each dose level. The effects of age and gender on the pharmacokinetics of Venofer have not been studied.

Pharmacokinetics in Pediatric Patients
In a single-dose pharmacokinetic study of Venofer in 11 patients ages 12 to 16 with NDD-CKD receiving or not receiving erythropoiesis stimulating agents, patients received Venofer, 7 mg/kg (maximum 200 mg) as undiluted Venofer given via intravenous bolus administration over 5 minutes followed by 24 hours of follow-up for pharmacokinetic analysis and a contact at 30 days for safety follow-up. Total serum iron increased rapidly following the 5-minute intravenous bolus administration of the 7 mg/kg dose. After dosing, total serum iron exhibited bi-phasic kinetics with an elimination half-life of 8.04 hours. The observed mean C_{max} was 8545 μg/dL at 0.50 hours after dosing. There was one reported adverse event for mild, transient hypotension post-injection. No serious adverse events or deaths were reported.

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).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with iron sucrose.

Iron sucrose was not mutagenic *in vitro* in the bacterial reverse mutation assay (Ames test) or the mouse lymphoma assay. Iron sucrose was not clastogenic in the *in vitro* chromosome aberration assay using human lymphocytes or in the *in vivo* mouse micronucleus assay.

Iron sucrose at intravenous doses up to 15 mg/kg/day of elemental iron (1.2 times the maximum recommended human dose based on body surface area) had no effect on fertility and reproductive function of male and female rats.

14 CLINICAL STUDIES

Six clinical trials involving 647 patients were conducted to assess the safety and efficacy of Venofer.

14.1 Study A: Hemodialysis Dependent-Chronic Kidney Disease (HDD–CKD)
Study A was a multicenter, open-label, historically-controlled study in 101 patients with HDD-CKD (77 patients with Venofer treatment and 24 in the historical control group) with iron deficiency anemia. Eligibility criteria for Venofer treatment included patients undergoing chronic hemodialysis, receiving erythropoietin, hemoglobin level between 8.0 and 11.0 g/dL, transferrin saturation < 20%, and serum ferritin < 300 ng/mL. The mean age of the patients was 65 years with the age range of 31 to 85 years. Of the 77 patients, 44 (57%) were male and 33 (43%) were female.

Venofer 100 mg was administered at 10 consecutive dialysis sessions either as slow injection or a slow infusion. 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 to 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 level were similar between treatment and historical control patients.

Patients in the Venofer treated population showed a greater increase in hemoglobin and hematocrit than did patients in the historical control population. See Table 2.

Table 2. 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 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 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%).

14.2 Study B: Hemodialysis Dependent-Chronic Kidney Disease (HDD-CKD)

Study B was a multicenter, open label study of Venofer in 23 patients with iron deficiency and HDD-CKD who had been discontinued from iron dextran due to intolerance. Eligibility criteria were otherwise identical to Study A. The mean age of the patients in this study was 53 years, with ages ranging from 21 to 79 years. Of the 23 patients enrolled in the study, 10 (44%) were male and 13 (56%) were female.

All 23 enrolled patients were evaluated for efficacy. 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.

14.3 Study C: Hemodialysis Dependent-Chronic Kidney Disease (HDD-CKD)

Study C was a multicenter, open-label study in patients with HDD-CKD. This study enrolled patients with a hemoglobin ≤ 10 g/dL, a serum transferrin saturation ≤ 20%, and a serum ferritin ≤ 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 to 70 years. Of 130 patients evaluated for efficacy in this study, 68 (52%) were male and 62 (48%) were female. 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. A 50 mg dose (2.5 mL) was given to patients within two weeks of study entry as a test dose. 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.

The modified intention-to-treat (mITT) population consisted of 131 patients. 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 increased at week 4 of the observation period.

14.4 Study D: Non-Dialysis Dependent-Chronic Kidney Disease (NDD-CKD)

Study D was a randomized, open-label, multicenter, active-controlled study of the safety and efficacy of oral iron versus Venofer in patients with NDD-CKD with or without erythropoietin therapy. Erythropoietin therapy was stable for 8 weeks prior to randomization. In the study 188 patients with NDD-CKD, hemoglobin of ≤ 11.0 g/dL, transferrin saturation ≤ 25%, ferritin ≤ 300 ng/mL were randomized to receive oral iron (325 mg ferrous sulfate three times daily for 56 days); or Venofer (either 200 mg over 2 to 5 minutes 5 times within 14 days or two 500 mg infusions on Day 1 and Day 14, administered over 3.5 to 4 hours). The mean age of the 91 treated patients in the Venofer group was 61.6 years (range 25 to 86 years) and 64 years (range 21 to 86 years) for the 91 patients in the oral iron group.

A statistically significantly greater proportion of Venofer subjects (35/79; 44.3%) compared to oral iron subjects (23/82; 28%) had an increase in hemoglobin ≥ 1 g/dL at anytime during the study ($p = 0.03$).

14.5 Study E: Peritoneal Dialysis Dependent-Chronic Kidney Disease (PDD-CKD)

Study E was a randomized, open-label, multicenter study comparing patients with PDD-CKD receiving an erythropoietin and IV iron to patients with PDD-CKD receiving an erythropoietin alone without iron supplementation. Patients with PDD-CKD, stable erythropoietin for 8 weeks, hemoglobin of ≤ 11.5 g/dL, TSAT ≤ 25%, ferritin ≤ 500 ng/mL were randomized to receive either no iron or Venofer (300 mg in 250 mL 0.9% NaCl over 1.5 hours on Day 1 and 15 and 400 mg in 250 mL 0.9% NaCl over 2.5 hours on Day 29). The mean age of the 75 treated patients in the Venofer / erythropoietin group was 51.9 years (range 21 to 81 years) vs. 52.8 years (range 23 to 77 years) for 46 patients in the erythropoietin alone group.

Patients in the Venofer / erythropoietin group had statistically significantly greater mean change from baseline to the highest hemoglobin value (1.3 g/dL), compared to subjects who received erythropoietin alone (0.6 g/dL) ($p < 0.01$). A greater proportion of subjects treated with Venofer / erythropoietin (59.1 %) had an increase in hemoglobin of ≥ 1 g/dL at any time during the study compared to the subjects who received erythropoietin only (33.3%).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How supplied

Venofer is supplied sterile in 10 mL, 5 mL, and 2.5 mL single use vials. Each 10 mL vial contains 200 mg elemental iron, each 5 mL vial contains 100 mg elemental iron, and each 2.5 mL vial contains 50 mg elemental iron (20 mg/mL).

NDC-0517-2310-05	200 mg/10 mL Single Use Vial	Packages of 5
NDC-0517-2310-10	200 mg/10 mL Single Use Vial	Packages of 10
NDC-0517-2340-01	100 mg/5 mL Single Use Vial	Individually Boxed
NDC-0517-2340-10	100 mg/5 mL Single Use Vial	Packages of 10
NDC-0517-2340-25	100 mg/5 mL Single Use Vial	Packages of 25
NDC-0517-2325-10	50 mg/2.5 mL Single Use Vial	Packages of 10
NDC-0517-2325-25	50 mg/2.5 mL Single Use Vial	Packages of 25

16.2 Stability and storage

Contains no preservatives. Store in original carton at 25°C (77°F). Excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature]. Do not freeze.

Syringe Stability: Venofer, when diluted with 0.9% NaCl at concentrations ranging from 2 mg to 10 mg of elemental iron per mL, or undiluted (20 mg elemental iron per mL) and stored in a plastic syringe, was found to be physically and chemically stable for 4 hours at controlled room temperature (25°C ± 2°C) and 24 hours under refrigeration (4°C ± 2°C).

IV Admixture Stability: Venofer, when added to IV infusion bags (PVC or non-PVC) containing 0.9% NaCl at concentrations ranging from 1 mg to 2 mg of elemental iron per mL, has been found to be physically and chemically stable for 4 hours at controlled room temperature (25°C ± 2°C) and for 24 hours under refrigeration (4°C ± 2°C).

Do not dilute to concentrations below 1 mg/mL.

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 infusion.

17 PATIENT COUNSELING INFORMATION

Prior to Venofer administration:

- Question patients regarding any prior history of reactions to parenteral iron products
- Advise patients of the risks associated with Venofer
- Advise patients to report any symptoms of hypersensitivity that may develop during and following Venofer administration, such as rash, itching, dizziness, light-headedness, swelling, and breathing problems [*see Warnings and Precautions (5)*]

AMERICAN REGENT, INC.
SHIRLEY, NY 11967

IN2340
Rev. 6/2011
MG #15727

Venofer is manufactured under license from Vifor (International) Inc., Switzerland.