PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**VENOFER®**

Iron Sucrose Injection

Solution, 20 mg elemental Iron/mL (as iron sucrose),

Intravenous Use

USP

Iron, parenteral preparations

AMERICAN REGENT, INC.

5 Ramsey Road

Shirley, New York USA 11967
www.americanregent.com

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RECENT MAJOR LABEL CHANGES

7 Warnings and Precautions, 7.1.1 Pregnant Women	02/2023

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

VENOFER® (Iron Sucrose Injection) is indicated in the treatment of iron deficiency anemia in the following patients:

- non-dialysis-dependent chronic kidney disease (NDD-CKD) patients receiving an erythropoietin
- non-dialysis-dependent chronic kidney disease (NDD-CKD) patients not receiving an erythropoietin
- hemodialysis dependent chronic kidney disease (HDD-CKD) patients receiving an erythropoietin
- peritoneal dialysis dependent chronic kidney disease (PDD-CKD) patients receiving an erythropoietin.

1.1 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Clinical studies with VENOFER have not identified differences in unintended responses between elderly and younger patients. Nevertheless, dose selection for an elderly patient should be cautious, usually starting with lower doses, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

2 CONTRAINDICATIONS

- The use of VENOFER® is contraindicated in patients with evidence of iron overload and patients with anemia not caused by iron deficiency.
- VENOFER is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Serious hypersensitivity reactions including life-threatening and fatal anaphylactic/anaphylactoid reactions have been reported in patients receiving intravenous iron products including VENOFER (see **Immune, Hypersensitivity and Anaphylactic Reactions**).
- VENOFER should only be administered when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions (see **Immune, Hypersensitivity and Anaphylactic Reactions**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- 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).
- Most CKD patients will require a minimum cumulative dose of 1000 mg of elemental iron, administered over sequential sessions, to achieve a favourable hemoglobin or hematocrit response. Patients may then continue to require therapy at the lowest dose necessary to maintain target levels of hemoglobin, hematocrit and iron storage parameters within acceptable limits (ferritin, TSAT).
- Should hypersensitivity reactions or signs of intolerance occur, 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 resuscitative interventions are immediately available for the treatment of serious hypersensitivity reactions (see **7 WARNINGS AND PRECAUTIONS**).

4.2 Recommended Dose and Dosage Adjustment

Recommended Adult Dosage:

- **Non-Dialysis-Dependent Chronic Kidney Disease Patients (NDD-CKD):** VENOFER is administered as a total cumulative dose of 1000 mg over a 14 day period as a 200 mg slow IV injection undiluted over 2 to 5 minutes on 5 different occasions within the 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 - 4 hours on day 1 and day 14; hypotension occurred in 2 of 30 patients treated. Patients weighing less than 70 kg may require a longer infusion time.
- **Hemodialysis Dependent Chronic Kidney Disease Patients (HDD-CKD):** VENOFER may be administered undiluted as a 100 mg 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 for a total cumulative dose of 1000 mg.
- **Peritoneal Dialysis Dependent Chronic Kidney Disease Patients (PDD-CKD):** VENOFER is administered as a total cumulative dose of 1000 mg in 3 divided doses within a 28 day period: 2 infusions of 300 mg over 1.5 hours 14 days apart followed by one 400 mg infusion over 2.5 hours 14 days later. The VENOFER dose should be diluted in a maximum of 250 mL of 0.9% NaCl.

4.4 Administration

VENOFER must only be administered intravenously by slow injection or infusion.

Table 1 Dilution

Dose (mg Fe)	Nominal Concentration per mL	Volume of VENOFER to be Added to Diluent	Volume of Diluent
Non-Dialysis-Dependent Chronic Kidney Disease Patients (NDD-CKD):			
500 mg	2 mg/mL (when the maximum of 250 mL 0.9% NaCl is used).	25 mL	Maximum 250 mL 0.9% NaCl
Hemodialysis Dependent Chronic Kidney Disease Patients (HDD-CKD):			
100 mg	1 mg/mL (when the maximum of 100 mL 0.9% NaCl is used).	5 mL	Maximum 100 mL 0.9% NaCl
Peritoneal Dialysis Dependent Chronic Kidney Disease Patients (PDD-CKD):			
300 mg	1.2 mg/mL (when the maximum of 250 mL 0.9% NaCl is used).	15 mL	Maximum 250 mL 0.9% NaCl
400 mg	1.6 mg/mL (when the maximum of 250 mL 0.9% NaCl is used).	20 mL	Maximum 250 mL 0.9% NaCl

When prepared as an infusion, use immediately. Do not store. Infusion rate as outlined in **4.2 Recommended Dosage and Dosage Adjustment**.

Do not mix VENOFER with other medications or add to parenteral nutrient solutions for intravenous infusion. As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used. Discard unused portion (see **11 STORAGE, STABILITY AND DISPOSAL**).

4.5 Missed Dose

If a planned dose of VENOFER is missed, it should be administered as soon as possible. The schedule of administration should be adjusted to maintain the prescribed dosing interval.

5 OVERDOSAGE

In case of drug overdose, seek emergency medical attention, even if there are no symptoms.

Dosages of VENOFER in excess of iron needs may lead to the accumulation of iron in storage sites, resulting in 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 exceed usual norms (see **7 WARNINGS AND PRECAUTIONS – General**). 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 include 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, corticosteroids and/or antihistamines.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Solution, 20 mg elemental iron per mL (as iron sucrose)	Water for injection. Sodium hydroxide may be used to adjust the pH.

VENOFER® is a brown, viscous, sterile, nonpyrogenic, aqueous solution containing 20 mg elemental iron per mL in the form of an iron (III)-hydroxide sucrose complex as the active ingredient, and water for injection. Sodium hydroxide may be used to adjust the pH to 10.5 – 11.1. The sterile solution has an osmolarity of 1250 mOsmol/L. The product does not contain preservatives or dextran polysaccharides.

VENOFER is available in 5 mL single dose vials, sold in boxes of 10.

7 WARNINGS AND PRECAUTIONS

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.

General

Because body iron excretion is limited and excess tissue iron can be hazardous, caution should be exercised in the administration of parenteral iron formulations, and treatment should be withheld when there is evidence of tissue iron overload. Patients receiving VENOFER require periodic monitoring of hematologic parameters, including hemoglobin, hematocrit, serum ferritin and transferrin saturation. Generally accepted guidelines recommend withholding administration of intravenous iron formulations from patients demonstrating a transferrin saturation > 50% and or serum ferritin > 800 ng/mL (see **4 DOSAGE AND ADMINISTRATION** and **5 OVERDOSAGE**). Transferrin saturation values increase rapidly after IV administration of iron sucrose; thus, serum iron values may be reliably obtained 48 hours after IV dosing.

Local Reactions

Care must be taken to avoid paravenous infiltration. If this occurs, the infusion of VENOFER should be discontinued immediately. Ice may be applied to cause local vasoconstriction and decrease fluid

absorption; massage of the area should be avoided.

Carcinogenesis and Mutagenesis

No data in humans is available. See animal data in **16 NON-CLINICAL TOXICOLOGY**.

Cardiovascular

VENOFER may cause clinically significant hypotension. Hypotension has been reported frequently in hemodialysis dependent chronic kidney disease patients receiving intravenous iron. Hypotension also has been reported in non-dialysis-dependent (NDD-CK) and peritoneal dialysis dependent (PDD-CK) chronic kidney disease patients receiving intravenous iron. Hypotension following administration of VENOFER may be related to the rate of administration and total dose administered. Caution should be taken to administer VENOFER according to recommended guidelines. See **4 DOSAGE AND ADMINISTRATION**. Monitor for signs and symptoms of hypotension following each administration of VENOFER.

Immune

Hypersensitivity and Anaphylactic Reactions

Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving VENOFER. Several cases of mild to moderate hypersensitivity reactions characterized by wheezing, dyspnea, hypotension, rash and/or pruritus were observed in pivotal and post-market studies. Although very rare, anaphylactic/anaphylactoid reactions have been reported in worldwide clinical safety studies and spontaneous post-marketing reports (also see **8 ADVERSE REACTIONS**).

Should hypersensitivity reactions or signs of intolerance occur, stop VENOFER immediately. Most reactions associated with intravenous iron preparations occur within 30 minutes of the completion of the infusion. 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 resuscitative interventions are immediately available for the treatment of serious hypersensitivity reactions (see **4 DOSAGE AND ADMINISTRATION**).

Reproductive Health: Female and Male Potential

- **Fertility**

  VENOFER at IV doses up to 15 mg iron/kg/dose (about 10 times the maximum recommended human dose for a 70 kg person) given three times a week was found to have no effect on fertility and reproductive performance of male and female rats.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well controlled studies in pregnant women.

Because animal reproduction studies are not always predictive of human response, VENOFER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratology studies performed in rats at IV doses up to 13 mg iron/kg/day (more than 9 times the maximum recommended human dose for a 70 kg person) and rabbits at IV doses up to 13 mg iron/kg on alternate days (approximately 9 times the maximum recommended human dose for a 70 kg person)

have not revealed definitive evidence of impaired fertility. Fetal growth effects at these doses appeared related to low maternal food consumption and low body weight gain.

When iron sucrose was administered at deliberate overdoses to rabbit dams (up to 215 mg/kg/day) marked fetal/placental iron overload was noted. It is unlikely that significant fetal iron overload would occur in iron deficient pregnant women receiving therapeutic doses of VENOFER to correct iron deficiency (see **7 WARNINGS AND PRECAUTIONS – General**).

Fetal bradycardia may occur following administration of parenteral irons. It is usually transient and a consequence of a hypersensitivity reaction in the mother. Patients should be advised of the potential risk to the fetus. If intravenous administration of parenteral irons to pregnant women is considered, the unborn baby should be carefully monitored.

7.1.2 Breast-feeding

VENOFER is excreted in the milk of rats. It is not known whether VENOFER is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VENOFER is administered to nursing women.

7.1.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use. 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.

7.1.4 Geriatrics (> 65 years of age)

Clinical studies with VENOFER have not identified differences in unintended responses between elderly and younger patients. Nevertheless, dose selection for an elderly patient should be cautious, usually starting with lower doses, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common treatment-related adverse events were dysgeusia, hypotension [not otherwise specified (NOS)], nausea, and dizziness.

In the HDD-CKD clinical indication group, the most common treatment-related adverse event was hypotension NOS. In the NDD-CKD clinical indication group, the most common treatment-related adverse event was dysgeusia in the VENOFER® group. In the PDD-CKD clinical indication group, the most common event in the VENOFER group was diarrhea.

The most common treatment-emergent adverse events related to study drug were hypotension NOS in the 100 mg dose group, dysgeusia in the 200 mg dose group, diarrhea NOS in the 300 mg and 400 mg dose groups, and peripheral edema, dizziness, and hypotension NOS in the 500 mg dose group.

No dose-related trends were noted for serious adverse events or premature discontinuations due to

adverse events. No clinically important incidence of hypersensitivity/allergic reaction was observed in the clinical studies.

Hypotension has been reported frequently in hemodialysis patients receiving IV iron.

Hypersensitivity Reactions: See **7 WARNINGS AND PRECAUTIONS**.

In clinical studies, several patients experienced hypersensitivity reactions presenting with wheezing, dyspnea, hypotension, rashes, or pruritus. Serious episodes of hypotension occurred in 2 patients treated with VENOFER at a dose of 500 mg.

One hundred thirty (11%) of the 1151 patients evaluated in the 4 U.S. trials in HDD-CKD patients (studies A, B and the two post marketing studies) had other prior 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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adverse Events observed in all treated populations

The frequency of adverse events associated with the use of VENOFER has been documented in six randomized clinical trials involving 231 hemodialysis dependent, 139 non-dialysis-dependent, and 75 peritoneal dialysis dependent patients; and in two post-marketing safety studies involving 1051 hemodialysis dependent patients, for a total of 1496 patients. In addition, over 2000 patients treated with VENOFER have been reported in the medical literature.

Treatment-emergent adverse events reported by ≥ 2% of treated patients in the randomized clinical trials, whether or not related to VENOFER administration, are listed by indication in Table 3.

Table 3 – Most Common Treatment-Emergent Adverse Events Reported in ≥ 2% of Patients by Clinical Indication (Multidose Safety Population)

Adverse Events (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 event	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

Adverse Events (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) %
Gastrointestinal Disorders					
Abdominal pain NOS	3.5	1.4	2.9	4.0	6.5
Constipation	1.3	4.3	12.9	4.0	6.5
Diarrhea NOS	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 NOS	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
Edema NOS	0.4	6.5	6.5	0	2.2
Fatigue	1.7	3.6	5.8	0	4.3
Feeling abnormal	3.0	0	0	0	0
Infusion site burning	0	3.6	0	0	0
Injection site extravasation	0	2.2	0	0	0
Injection site pain	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					
Catheter site infection	0	0	0	4.0	8.7
Nasopharyngitis	0.9	0.7	2.2	2.7	2.2
Peritoneal infection	0	0	0	8.0	10.9
Sinusitis NOS	0	0.7	0.7	4.0	0
Upper respiratory tract infection NOS	1.3	0.7	1.4	2.7	2.2
Urinary tract infection NOS	0.4	0.7	5.0	1.3	2.2
Injury, Poisoning and Procedural Complications					
Graft complication	9.5	1.4	0	0	0
Investigations					
Cardiac murmur NOS	0.4	2.2	2.2	0	0
Fecal occult blood positive	0	1.4	3.6	2.7	4.3

Adverse Events (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) %
Metabolism and Nutrition Disorders					
Fluid overload	3.0	1.4	0.7	1.3	0
Gout	0	2.9	1.4	0	0
Hyperglycemia NOS	0	2.9	0	0	2.2
Hypoglycemia NOS	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
Arthritis NOS	0	0	0	0	4.3
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
Hypoesthesia	0	0.7	0.7	0	4.3
Respiratory, Thoracic and Mediastinal Disorders					
Cough	3.0	2.2	0.7	1.3	0
Dyspnea	3.5	3.6	0.7	1.3	2.2
Dyspnea exacerbated	0	2.2	0.7	0	0
Nasal congestion	0	1.4	2.2	1.3	0
Pharyngitis	0.4	0	0	6.7	0
Rhinitis allergic NOS	0	0.7	2.2	0	0
Skin and Subcutaneous Tissue Disorders					
Pruritus	3.9	2.2	4.3	2.7	0
Rash NOS	0.4	1.4	2.2	0	2.2
Vascular Disorders					
Hypertension NOS	6.5	6.5	4.3	8.0	6.5
Hypotension NOS	39.4	2.2	0.7	2.7	2.2

Treatment-emergent adverse events reported in ≥2% of patients by dose group are shown in Table 4.

Table 4 – Most Common Treatment-Emergent Adverse Events Reported in ≥2% of Patients by Clinical Indication and Dose Group (Multidose Safety Population)

Adverse Events (Preferred Term)	HDD-CKD	NDD-CKD		PDD-CKD
	100 mg (N=231) %	200 mg (N=109) %	500 mg (N=30) %	300 mg for 2 doses followed by 400 mg for 1 dose (N= 75) %
Subjects with any adverse event	78.8	75.2	80.0	72.0
Ear and Labyrinth Disorders				
Ear pain	0	0.9	6.7	0
Eye Disorders				
Conjunctivitis	0.4	0	0	2.7
Gastrointestinal Disorders				
Abdominal pain NOS*	3.5	1.8	0	4.0
Constipation	1.3	3.7	6.7	4.0
Diarrhea NOS	5.2	6.4	10.0	8.0
Dysgeusia	0.9	9.2	3.3	0
Nausea	14.7	9.2	6.7	5.3
Vomiting NOS	9.1	5.5	3.3	8.0
General Disorders and Administration Site Conditions				
Asthenia	2.2	0.9	0	2.7
Chest pain	6.1	0.9	3.3	2.7
Edema NOS	0.4	7.3	3.3	0
Fatigue	1.7	4.6	0	0
Feeling abnormal	3.0	0	0	0
Infusion site burning	0	3.7	3.3	0
Injection site pain	0	2.8	0	0
Peripheral edema	2.6	5.5	13.3	5.3
Pyrexia	3.0	0.9	0	1.3
Infections and Infestations				
Catheter site infection	0	0	0	4.0
Nasopharyngitis	0.9	0.9	0	2.7
Peritoneal infection	0	0	0	8.0
Sinusitis NOS	0	0	3.3	4
Upper respiratory tract infection	1.3	0.9	0	2.7

Adverse Events (Preferred Term)	HDD-CKD	NDD-CKD		PDD-CKD
	100 mg (N=231) %	200 mg (N=109) %	500 mg (N=30) %	300 mg for 2 doses followed by 400 mg for 1 dose (N= 75) %
Injury, Poisoning and Procedural Complications				
Graft complication	9.5	1.8	0	0
Investigations				
Cardiac murmur NOS	0.4	2.8	0	0
Fecal occult blood positive	0	1.8	0	2.7
Metabolism and Nutrition Disorders				
Fluid overload	3.0	1.8	0	1.3
Gout	0	1.8	6.7	0
Hyperglycemia NOS	0	3.7	0	0
Hypoglycemia NOS	0.4	0.9	0	4.0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	3.5	0.9	3.3	4.0
Back pain	2.2	1.8	3.3	1.3
Muscle cramp	29.4	0	3.3	2.7
Myalgia	0	2.8	6.7	1.3
Pain in extremity	5.6	4.6	3.3	2.7
Nervous System Disorders				
Dizziness	6.5	5.5	10.0	1.3
Headache	12.6	3.7	0	4.0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	3.0	0.9	6.7	1.3
Dyspnea	3.5	1.8	10.0	1.3
Pharyngitis	0.4	0	0	6.7
Skin and Subcutaneous Tissue Disorders				
Pruritus	3.9	0.9	6.7	2.7
Vascular Disorders				
Hypertension NOS	6.5	6.4	6.7	8.0
Hypotension NOS	39.4	0.9	6.7	2.7

* NOS=not otherwise specified

Drug related adverse events reported by ≥2% of VENOFER treated patients are shown by dose group in Table 5.

Table 5 – Most Common Adverse Events Related to Study Drug Reported in ≥ 2% of Patients by Clinical Indication and Dose Group (Multidose Safety Population)

Adverse Events (Preferred Term)	HDD-CKD	NDD-CKD		PDD-CKD
	100 mg (N=231) %	200 mg (N=109) %	500 mg (N=30) %	300 mg for 2 doses followed by 400 mg for 1 dose (N= 75) %
Subjects with any adverse event	14.7	23.9	20.0	10.7
Gastrointestinal Disorders				
Diarrhea NOS*	0.9	0	0	2.7
Dysgeusia	0.9	7.3	3.3	0
Nausea	1.7	2.8	0	1.3
General Disorders and Administration Site Conditions				
Infusion site burning	0	3.7	0	0
Injection site pain	0	2.8	0	0
Peripheral edema	0	1.8	6.7	0
Nervous Systems Disorders				
Dizziness	0	2.8	6.7	0
Headache	0	2.8	0	0
Vascular Disorders				
Hypotension NOS*	5.2	0	6.7	0

* NOS=not otherwise specified

Adverse Events Observed in Hemodialysis Dependent Chronic Kidney Disease (HDD-CKD)

Adverse reactions, whether or not related to VENOFER administration, reported by >5% of treated patients from a total of 231 patients in HDD-CKD Studies A, B, and C were as follows: hypotension (39.4%), muscle cramps (29.4%), nausea (14.7%), headache (12.6%), graft complications (9.5%), vomiting (9.1%), dizziness (6.5%), hypertension (6.5%), chest pain (6.1%), and diarrhea (5.2%).

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. In this 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. 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%), Hispanics (11%), Asians (3%), and others (1%). Adverse events reported by >1% of 1051 treated patients were: cardiac failure congestive, sepsis NOS and dysgeusia.

Adverse Events Observed in Non-Dialysis-Dependent Chronic Kidney Disease (NDD-CKD) Patients

In Study D of 182 treated NDD-CKD patients, 91 were exposed to VENOFER. Adverse events, whether or not related to VENOFER, reported by ≥5% of the VENOFER exposed patients were as follows: dysgeusia (7.7%), peripheral edema (7.7%), diarrhea (5.5%), constipation (5.5%), nausea (5.5%), dizziness (5.5%), and hypertension (5.5%). One serious related adverse reaction was reported (hypotension and shortness of breath not requiring hospitalization in a VENOFER patient). Two patients experienced possible hypersensitivity/allergic reactions (local edema/hypotension) during the study. Of the 5 patients who prematurely discontinued the treatment phase of the study due to adverse events (2 oral iron group and 3 VENOFER group), three VENOFER patients had events that were considered drug-related (hypotension, dyspnea and nausea).

In an additional study of VENOFER with varying erythropoietin doses in 96 treated NDD-CKD patients, adverse events, whether or not related to VENOFER, reported by ≥5% of VENOFER exposed patients are as follows: diarrhea (16.5%), edema (16.5%), nausea (13.2%), vomiting (12.1%), arthralgia (7.7%), back pain (7.7%), headache (7.7%), hypertension (7.7%), dysgeusia (7.7%), dizziness (6.6%), extremity pain (5.5%), and injection site burning (5.5%). No patient experienced a hypersensitivity/allergic reaction during the study. Of the patients who prematurely discontinued the treatment phase of the study due to adverse events (2.1% oral iron group and 12.5% VENOFER group), only one patient (VENOFER group) had events that were considered drug-related (anxiety, headache, and nausea). Ninety-one (91) patients in this study were exposed to VENOFER either during the treatment or extended follow-up phase.

Adverse Events Observed in Peritoneal Dialysis Dependent Chronic Kidney Disease (PDD-CKD)

In Study E of 121 treated PDD-CKD patients, 75 were exposed to VENOFER. Adverse events, whether or not related to VENOFER, reported by ≥5% of these patients were as follows: vomiting (8.0%), diarrhea (8.0%), hypertension (8.0%), peritoneal infection (8.0%), pharyngitis (6.7%), nausea (5.3%) and peripheral edema (5.3%). The only drug related adverse reaction to VENOFER administration reported by ≥2% of patients was diarrhea (2.7%). No serious drug related adverse reactions were reported during the treatment phase of study. Two VENOFER patients experienced a moderate hypersensitivity / allergic reaction (rash or swelling/itching) during the study. Three patients in the VENOFER study group discontinued study treatment due to adverse events (cardiopulmonary arrest, peritonitis, myocardial infarction, hypertension) which were considered to be not drug-related.

8.5 Post-Market Adverse Reactions

Hypersensitivity Reactions: Based on data from the post-marketing spontaneous reporting system and literature, the relative prevalence of anaphylactoid reactions was estimated at 0.0023% (116 anaphylactoid reactions out of an exposure of 5,123,048 patient-years to VENOFER). Some of these reactions were serious or life-threatening, including anaphylactic shock, loss of consciousness or collapse, bronchospasm with dyspnea, or convulsion (See **3 SERIOUS WARNINGS AND PRECAUTIONS BOX** and **7 WARNINGS AND PRECAUTIONS**).

Cardiac disorders:

Fetal bradycardia due to maternal hypersensitivity reactions, tachycardia

General disorders and administration site conditions:

Chills, feeling hot, influenza-like illness, injection site reaction, malaise

Investigations:

Blood iron abnormal, pulmonary test decreased

Musculoskeletal and connective tissue disorders:

Arthritis, Bone pain

Nervous system disorders:

Burning sensation, loss of consciousness, paraesthesia

Pregnancy, puerperium and perinatal conditions:

Abortion

Respiratory, thoracic and mediastinal disorders:

Asthma, respiratory failure, throat tightness

Skin and subcutaneous tissue disorders:

Erythema, exanthema, urticaria, skin discolouration

Vascular disorders:

Circulatory collapse, flushing

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Drug interactions involving VENOFER have not been studied.

Oral iron should not be administered concomitantly with parenteral iron preparations. Like other parenteral iron preparations, VENOFER may be expected to reduce the absorption of concomitantly administered oral iron preparations.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Iron sucrose is used to replenish body iron stores in dialysis dependent and non-dialysis-dependent chronic kidney disease (NDD-CKD) patients. Iron deficiency may be caused by blood loss during dialysis, increased erythropoiesis secondary to erythropoietin use, 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 the physiologically important heme and non-heme compounds. Most dialysis patients require intravenous iron to maintain sufficient iron stores.

10.2 Pharmacodynamics

Following intravenous administration of VENOFER, iron sucrose is dissociated by the reticuloendothelial system into iron and sucrose. In 22 chronic hemodialysis patients on erythropoietin therapy who completed treatment with iron sucrose at 100 mg of iron three times weekly for three weeks, significant increases in serum iron (12.8 µg/dL) and serum ferritin (266.3 ng/mL) and significant decreases in total iron binding capacity (-46.7 µg/dL) occurred four weeks from the initiation of iron sucrose treatment. Eligibility for this study included hemoglobin <11 g/dL and a ferritin ≤800 ng/mL or TSAT ≥50%. The mean patient age in the 23 treated (10 male and 13 female) patients was 53 years (range 21-79), mean weight 70.9 kg (range of 43-112 kg), mean hemoglobin 10.4 g/dL and mean baseline serum ferritin 50.7 ng/mL.

10.3 Pharmacokinetics

In healthy adults treated with intravenous doses of VENOFER, the 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, steady state apparent volume of distribution of 7.9 L, and the initial volume of distribution (Vdc) of 3.2 L.

In 12 adults (11 females and 1 male) with iron deficiency anemia (ferritin < 20 ng/L, hemoglobin between 9.0 to 13.5 g/dL in males and 9.0 to 12.5 g/dL in females) treated with 7 mg of iron per kg body weight (maximum 500 mg of iron) intravenous doses of VENOFER over 2.5 to 3.5 hours, the iron component had a total clearance of 0.64 L/h, steady state apparent volume of distribution of 11.4 L and the initial volume of distribution (Vd_c) of 3.4 L. The total clearance was lower following the 500 mg dose than following the 100 mg dose. The volumes of distribution were comparable to the results obtained in the non anemic patients.

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 compared to healthy individuals.

Distribution:

In healthy adults treated with intravenous doses of VENOFER, the iron component appears to distribute mainly in blood and to some extent in extravascular fluid. In a study evaluating VENOFER at 100 mg of iron labelled with $^{52}Fe/^{59}Fe$ in patients with iron deficiency, it was found that a significant amount of the administered iron distributes in the liver, spleen and bone marrow. The bone marrow is an iron trapping compartment and not a reversible volume of distribution.

Metabolism

VENOFER is dissociated by the reticuloendothelial system into iron and sucrose.

Elimination

The sucrose component of VENOFER 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. About 5% of the iron was eliminated via renal excretion over 24 h.

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 level of detection of the assay (less than 2 ppm).

Special Populations and Conditions

The effects of age and gender on the pharmacokinetics of VENOFER have not been studied.

11 STORAGE, STABILITY AND DISPOSAL

Store at 15-25°C. Do not freeze. Discard unused portion.

12 SPECIAL HANDLING INSTRUCTIONS

No special handling instructions are required for this product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Iron Sucrose

Chemical name: Iron (III)-hydroxide sucrose complex, Ferric-hydroxide Sucrose Complex, Saccharated Iron Oxide

Molecular formula and molecular mass: $[Na_2Fe_5O_8(OH) \bullet 3(H_2O)]_n \bullet m(C_{12}H_{22}O_{11})$ and approximately 43,200 daltons (n = the degree of iron polymerization and m = the number of sucrose molecules in complex with the iron (III)-hydroxide)

Structural formula: Exact structural formula not known.

Physicochemical properties: Iron sucrose is a brown, viscous, aqueous solution with a total iron content of 3.50 – 3.90% w/w and a pH of 10.5 – 11.0.

14 CLINICAL TRIALS

Five clinical trials were conducted to assess the safety and efficacy of VENOFER in adults. Four studies were conducted in the United States and one was conducted in South Africa.

14.1 Clinical Trials by Indication

Hemodialysis Dependent Chronic Kidney Disease (HDD-CKD)

Table 6 – Summary of patient demographics for clinical trials in Hemodialysis Dependent Chronic Kidney Disease (HDD-CKD)

Study	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study A	Multicenter, open-label, historically-controlled	VENOFER 5 mL (one vial) containing 100 mg of elemental iron was administered through the dialysis line at each dialysis session either as slow intravenous injection or a saline diluted slow infusion for a total of 10 dialysis sessions with a cumulative dose of 1000 mg elemental iron.	101	65 years (31-85)	57% male 43% female
Study B	Multicenter, open-label	VENOFER 5 mL (one vial) containing 100 mg of elemental iron was administered through the	23	53 years (21-79)	44% male 56% female

		dialysis line at each dialysis session either as slow intravenous injection or a saline diluted slow infusion for a total of 10 dialysis sessions with a cumulative dose of 1000 mg elemental iron.			
Study C	Multicenter, open-label, two period (treatment followed by observation period	VENOFER was administered in doses of 100 mg during sequential dialysis sessions until a pre-determined (calculated) total dose of iron was administered.	130	41 years (16-70)	52% male 48% female

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

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 level 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 and hematocrit were higher and erythropoietin dose was lower in the historical control population than in the VENOFER treated population.

Patients in the VENOFER treated population showed a statistically significant greater increase in hemoglobin and hematocrit than did patients in the historical control population. See Table 7.

Table 7 – 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.

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

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 (35%); Black (35%); Hispanic (26%); Asian (4%). 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: Hemodialysis Dependent Chronic Kidney Disease (HDD-CKD)

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 (23%); Black (23%); Asian (5%); Other (mixed ethnicity) (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.

Non-Dialysis-Dependent Chronic Kidney Disease (NDD-CKD)

Table 8 – Summary of patient demographics for clinical trials in Non-Dialysis-Dependent Chronic Kidney Disease (NDD-CKD)

Study	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study D	Randomized, open-label, multicenter, active-controlled	VENOFER either 200 mg over 2-5 minutes 5 times within 14 days or two 500 mg infusions on Day 1 and Day 14, administered over 3.5-4 hours.	188	VENOFER group (n=91): 61.6 years (range 25 to 86 years) Oral iron group (n=91): 64 years (range 21 to 86 years)	32% male 68% female

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 intravenous iron sucrose (VENOFER) in NDD-CKD patients with or without erythropoietin therapy. Erythropoietin therapy was stable for 8 weeks prior to randomization. In the study, 188 patients with NDD-CKD, transferrin saturation ≤25%, ferritin ≤300 ng/mL and an average baseline hemoglobin of ≤11.0 g/dL were randomized to receive oral iron (325 mg ferrous sulfate three times daily for 56 days) or VENOFER (either 200 mg over 2-5 minutes 5 times within 14 days or two 500 mg infusions on Day 1 and Day 14, administered over 3.5-4 hours). Of the 188 randomized patients, 182 were treated and followed for up to 56 days. Efficacy assessments were measured on days 14, 28, 42 and 56. 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. Ethnicity breakdown of the patients in the VENOFER group was as follows: Caucasian (60.4%), Black (34.1%), Hispanic (3.3%), Other (2.2%). Ethnicity breakdown for the oral iron group was: Caucasian (50.5%), Black (44.0%), Hispanic (4.4%), Other (1.1%). Patient demographic characteristics were not significantly different between the groups.

A statistically significant 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 any time during the study ($p=0.03$). In patients ≥65 years of age, the proportion of subjects achieving ≥1.0 g/dL increase in hemoglobin from baseline was 53% (20/38) in the VENOFER group compared to 23% (10/43) in the oral iron group. In patients <65 years of age, the proportion of subjects achieving ≥1.0 g/dL increase in hemoglobin from baseline was 37% (15/41) in the VENOFER group compared to 33% (13/39) in the oral iron group. A

statistically significant greater proportion of VENOFER treated patients (31/79; 39.2%) compared to oral iron treated patients (1/82; 1.2%) had an increase in hemoglobin ≥1 g/dL and ferritin ≥160 ng/mL at any time during the study (p<0.0001).

Table 9 – Results of Study D: Non-Dialysis-Dependent Chronic Kidney Disease (NDD-CKD)

Primary Endpoint	VENOFER	Oral iron
An increase in Hgb of at least 1.0 g/dL at any time between baseline and either the end of study or withdrawal.	44.3% of patients had an increase in Hgb ≥ 1 g/dL at any time during the study	28% of patients had an increase in Hgb ≥ 1 g/dL at any time during the study
	p-value=0.03	

Peritoneal Dialysis Dependent Chronic Kidney Disease (PDD-CKD)

Table 10 – Summary of patient demographics for clinical trials in Peritoneal Dialysis Dependent Chronic Kidney Disease (PDD-CKD)

Study	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study E	Randomized, open-label, multicenter	VENOFER (300 mg in 250 mL 0.9% NaCl over 1.5 hours on Day 1 and Day 15 and 400 mg in 250 mL 0.9% NaCl over 2.5 hours on Day 29)	126	VENOFER/erythropoietin group (n=75): 51.9 years (range 21 to 81 years) Erythropoietin alone group (n=46): 52.8 years (range 23 to 77 years)	58% male 42% female

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

Study E was a randomized [2:1 treatment:control], open-label, multicenter study comparing PDD-CKD patients receiving erythropoietin and IV iron to PDD-CKD patients receiving erythropoietin alone without iron supplementation. In the study 126 patients with PDD-CKD, stable erythropoietin for 8 weeks, transferrin saturation ≤ 25%, ferritin ≤ 500 ng/mL and an average baseline hemoglobin of ≤11.5 g/dL 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 Day 15 and 400 mg in 250 mL 0.9% NaCl over 2.5 hours on Day 29). Of the 126 randomized patients, 121 were treated and followed for up to 71 days. Efficacy assessments were measured on days 15, 29, 43, 57 and 71. The mean age of the 75 treated patients in the VENOFER/erythropoietin group was 51.9 years (range 21 to 81 years) and 52.8 years (range 23 to 77 years) for the 46 patients in the erythropoietin alone group. Ethnicity breakdown of the patients in the VENOFER/erythropoietin group was as follows: Black (21.3%), Caucasian (36.0%), Hispanic (32.0%), Other (10.7%). Ethnicity breakdown for the erythropoietin alone group was: Black (15.2%), Caucasian (30.4%), Hispanic (43.5%), Other (10.9%). Patient demographic characteristics were not significantly different between the groups.

Patients in the VENOFER/erythropoietin group had statistically significant 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=0.0028). Additionally, statistically significant greater mean changes from baseline to the highest ferritin and transferrin saturation values were observed for subjects who received VENOFER/erythropoietin (574.6 ng/mL and 18.2%, respectively) compared to subjects who received erythropoietin only (5.5 ng/mL and 10.4%, respectively) (p<0.0001 and p=0.0098, respectively). A statistically significant greater proportion of subjects treated with VENOFER/erythropoietin (59.1%) had an increase in hemoglobin of ≥1 g/dL during the study compared to the subjects who received erythropoietin only (33.3%) (p=0.0273).

Table 11 – Results of Study E: Peritoneal Dialysis Dependent Chronic Kidney Disease (PDD-CKD)

Primary Endpoint	VENOFER/erythropoietin	Erythropoietin only
Change from baseline to the highest Hb observed at any time between baseline and either the end of study or withdrawal	1.3 g/dL	0.6 g/dL
	p-value=0.0028	

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Acute toxicity studies in mice and rats indicated that intravenously administered iron sucrose was non-lethal at doses below 75 mg iron/kg. The LD_{50} of IV iron sucrose was lower for rats than mice and for male rats compared with female rats, with that of male rats being 140 mg iron/kg, and that of females 236 mg iron/kg.

In repeat-dosing studies in both beagles and rats, no mortality was seen at doses up to 30 mg iron/kg, administered over 1 hour three times a week for 13 weeks. Signs of toxicity from iron overload were seen in the liver, spleen and kidneys at 10 and 30 mg iron/kg.

In the beagles, liver and spleen enlargement was observed in most dogs receiving the 30 mg iron/kg dose, and liver enlargement was seen in most males receiving 10 mg iron/kg. There was a clear dose-related increase in the liver weight for both sexes, with some exceptionally high individual values, particularly at 30 mg iron/kg/dose. Group mean spleen weight was increased to a statistically significant degree for both sexes receiving the 30 mg iron/kg/dose. Dose-related iron deposition was observed mainly within macrophages and primarily in the liver, spleen and kidneys. In the liver, increased perivascular fibrosis and associated cellularity were seen at all doses and hepatocyte necrosis was noted at the 30 mg iron/kg dose. Extramedullary hematopoiesis was noted in the liver and spleen in dogs receiving 10 or 30 mg iron/kg/dose.

The non-toxic dose in rats and dogs was considered to be 3 mg iron/kg/dose administered three times weekly [9 mg iron/kg/week].

In a dog study with a seven-year observation period, hematological changes were widely evident following red cell transfusion or IV administration of 100-300 mg iron as iron sucrose five times a week for 6-10 weeks. Liver function tests and histopathology did not demonstrate cirrhosis. Tissue iron overload was well tolerated in these dogs with the notable exception of the development of blindness in all animals due to retinal changes resembling retinitis pigmentosa beginning about 3 years after iron

administration.

Carcinogenicity: No long-term studies in animals have been performed to evaluate the carcinogenic potential of VENOFER.

Genotoxicity: The Ames test, with or without metabolic activation, in vitro mouse lymphoma forward mutation test, mouse micronucleus test, and in vitro human lymphocyte chromosome aberration test were conducted with iron sucrose. No mutagenicity or genotoxicity was demonstrated.

Reproductive and Developmental Toxicology: VENOFER at IV doses up to 15 mg iron/kg/dose [about 10 times the maximum recommended human dose for a 70 kg person] given three times a week was found to have no effect on fertility and reproductive performance of male and female rats.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrVENOFER®

Iron Sucrose Injection

Read this carefully before you receive **VENOFER** and each time you receive VENOFER. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **VENOFER**.

Serious Warnings and Precautions

- Injectable iron products including VENOFER can cause serious allergic reactions, including fatal anaphylaxis or anaphylactoid reactions.
- You will receive VENOFER in a healthcare setting where staff is able to treat severe allergic reactions without delay. You will be monitored for signs and symptoms of an allergic reaction during and after your treatment with VENOFER.

What is VENOFER used for?

- VENOFER is used to treat iron deficiency anemia. This condition occurs when your body does not have enough iron. VENOFER is used in people with chronic kidney disease managed with or without dialysis.

How does VENOFER work?

VENOFER (iron sucrose) works by replenishing your body's iron levels. You need iron to make hemoglobin, which allows red blood cells to carry oxygen throughout your body.

What are the ingredients in VENOFER?

Medicinal ingredients: Iron sucrose

Non-medicinal ingredients: Water for injection. May contain sodium hydroxide to adjust pH.

VENOFER comes in the following dosage forms:

Solution: 20 mg elemental iron per mL (as iron sucrose)

Do not receive VENOFER if:

- you have any of these health problems:
  - too much iron in your body (iron overload)
  - anemia from a cause other than low iron
- you are allergic (hypersensitive) to iron sucrose or any of the other ingredients of VENOFER (See What are the ingredients in VENOFER)?

To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive VENOFER. Talk about any health conditions or problems you may have, including if you:

- have had any allergy to iron medicines given through a vein like VENOFER in the past.
- are pregnant or planning to become pregnant.
- are breastfeeding or planning to breastfeed. Animal studies show that VENOFER may pass into breast milk.

Other warnings you should know about:

Older people: Your healthcare professional will start with a lower dose of VENOFER to prevent side effects.

Pregnancy: Tell your healthcare professional right away if you are pregnant, become pregnant, think you are pregnant or are planning on becoming pregnant. You can have a serious allergic reaction while receiving VENOFER, which can cause serious harm to your unborn baby. They may develop an unusually slow heart rate. This usually lasts for a short time. If you are receiving this medicine while pregnant, your healthcare professional should carefully monitor your unborn baby.

Monitoring, Lab and blood tests: Your healthcare professional will do blood tests before you receive VENOFER and/or during treatment to monitor your progress or check for side effects. These tests and monitoring may include:

- checking your blood iron level in order to prevent iron overload (see Overdose below for signs of too much iron in your body)
- watching you closely for signs of
    - serious allergic reactions.
    - low blood pressure like dizziness or passing out

    See the **Serious side effects and what to do about them** table, below

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with VENOFER:

- iron pills taken by mouth (oral iron preparations). These may not work if you take them at the same time that you receive VENOFER.

How you will receive VENOFER:

- in a healthcare setting where staff can provide emergency medical treatment for allergic reactions. Your healthcare professional will watch you carefully while you receive each dose of VENOFER and for at least 30 minutes afterwards.
- as an injection into your vein. It is usually injected over 2 to 5 minutes or may be mixed with another fluid and injected slowly (infused) over 15 minutes to 4 hours depending on your dose of medication.

Usual dose:

Your healthcare professional will work out:

- the right dose of VENOFER for you.
- how often you receive VENOFER; Your total number of doses is based on your condition and how well you respond to the medication.

Overdose:

Signs of too much iron in your body (iron overload) due to VENOFER may include:
low blood pressure, headache, vomiting, nausea, dizziness, joint aches, a burning, pricking or tingling feeling, abdominal and muscle pain, swelling, and sudden drop in blood flow through the body (cardiovascular collapse or shock).

If you think you, or a person you are caring for, have received too much VENOFER, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss your scheduled dose, contact your healthcare professional as soon as possible to schedule your next treatment.

What are possible side effects from using VENOFER?

These are not all the possible side effects you may have when taking VENOFER. If you experience any side effects not listed here, tell your healthcare professional.

Common side effects that may occur include:

- nausea, vomiting, diarrhea, stomach pain, change in taste (everything seems sour, sweet, bitter or metallic)
- dizziness
- headache
- fever
- chest pain
- muscle cramps (especially leg cramps)
- swollen arm or leg
- general feeling of discomfort, flu-like symptoms such as: chills, headache, fatigue, muscle aches, or low-grade fever
- pain, redness or swelling at the injection site where the shot was given
- swelling of joints, bone pain
- burning or tingling sensation
- skin problems: skin rash, skin itchiness, skin discoloration
- flushing

If these become bothersome, consult your healthcare professional.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Hypotension (low blood pressure): dizziness, passing out, light-headedness, nausea, vomiting, fatigue		Y	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Peripheral edema (swelling of the legs or hands caused by fluid retention): swollen or puffy legs or hands		Y	
UNKNOWN			
Hypersensitivity reactions (allergic reactions) – which is sometimes life-threatening: fever, joint pain, nausea, vomiting, chest pain, rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			Y
Breathing problems: shortness of breath, difficult to breathe on your own (respiratory failure)			Y
Circulatory collapse (problems with the circulatory system which is made up of blood vessels that carry blood away from and towards the heart): severely low blood pressure, chest pain, passing out			Y

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store VENOFER at room temperature (15-25°C) until your appointment. Do not freeze. Discard unused portion.

Keep out of reach and sight of children.

If you want more information about VENOFER:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.americanregent.com, or by calling 1-800-1-800-645-1706.

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