PRODUCT MONOGRAPH

Pr VENOFER®

Iron Sucrose injection, USP

5 mL Single Dose Vials, 20 mg elemental iron/mL

Hematinic

Manufactured by:

Luitpold Pharmaceuticals, Inc.
One Luitpold Drive, P.O. Box 9001
Shirley, New York 11967

Date of Revision:
January 15, 2013

Distributed by:

Bellco Health Care Inc.
2900 Argentia Road, Unit 10
Mississauga, Ontario
Canada L5N 7X9

Control number: 159456

Table of Contents

VENOFER®

iron sucrose injection, USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
intravenous	5 mL Single Dose Vials, 20 mg elemental iron/mL	water for injection *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

VENOFER (Iron Sucrose Injection, USP) 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.

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.

Pediatrics:
The safety and effectiveness of VENOFER in pediatric patients has not been established.

CONTRAINDICATIONS

The use of VENOFER (Iron Sucrose Injection, USP) is contraindicated in patients with evidence of iron overload, patients with known hypersensitivity to VENOFER, and patients with anemia not caused by iron deficiency.

WARNINGS AND PRECAUTIONS

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 Hypersensitivity and Anaphylactic Reactions below).

- VENOFER should only be administered when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions (see Hypersensitivity and Anaphylactic Reactions below).

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 (Iron Sucrose Injection, USP) require periodic monitoring of hematologic parameters, including haemoglobin, 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 **DOSAGE AND ADMINISTRATION** and **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 long-term studies in animals have been performed to evaluate the carcinogenic potential of VENOFER.

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.

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 **DOSAGE AND ADMINISTRATION**. Monitor for signs and symptoms of hypotension following each administration of VENOFER.

Hypersensitivity Reactions 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(oid) reactions have been reported in worldwide clinical safety studies and spontaneous post-marketing reports (also see **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 **DOSAGE AND ADMINISTRATION)**.

Sexual Function/Reproduction
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.

Special Populations
Pregnant Women: 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. There are, however, 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.

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 **General**).

Nursing Women: 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.

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

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.

ADVERSE REACTIONS

Adverse Drug 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 events were 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.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse

events and for approximating rates.

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 1.

Table 1 – Most Common Treatment-Emergent Adverse Events Reported in ≥ 2% of Patients by Clinical Indication (Multidose Safety Population)

	HDD-CKD	NDD-CKD		PDD-CKD	
Adverse Events (Preferred Term)	**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
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

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) %
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
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 2.

Table 2. Most Common Treatment-Emergent Adverse Events Reported in ≥ 2% of Patients by Dose Group (Multidose Safety Population)			
	HDD-CKD	**NDD-CKD**	**PDD-CKD**

Adverse Events (Preferred Term)	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
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

Table 2. Most Common Treatment-Emergent Adverse Events Reported in ≥ 2% of Patients by 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) %
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 3.

Table 3. Most Common Adverse Events Related to Study Drug Reported in ≥ 2% of Patients by 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				

Table 3. Most Common Adverse Events Related to Study Drug Reported in ≥ 2% of Patients by 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) %
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.

Hypersensitivity Reactions: See **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.

Post-Market Adverse Drug Reactions

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

From the post-marketing spontaneous reporting system, there were 108 reports of anaphylactoid reactions including patients who experienced serious or life-threatening reactions (anaphylactic shock, loss of consciousness or collapse, bronchospasm with dyspnea, or convulsion) associated with VENOFER administration between 1992 and August, 2005, based on estimated use in more than 4.6 million patients.

Among the 517,736 patients (estimated on the basis of 10,354,715 ampoules sold) who received VENOFER between September 1, 2005 and February 28, 2006 through market exposure, 61 patients were reported to have experienced 104 adverse reactions considered at least "possibly related" to VENOFER. A review of all the symptoms concluded that 90 symptoms are listed, 38 serious and 52 non-serious; 14 symptoms are unlisted, 5 serious and 9 non-serious.

Considering the number of patients exposed to VENOFER, the number of adverse events at least possibly related to the product has been very limited. There was a moderate decrease in the frequency of unlisted symptoms and no changes in the nature of the listed ones. During this period no overdose of misuse have been reported.

Regarding the **serious and listed** cases, no particular change or trend in severity, outcome or involved populations could be observed. A total of 38 adverse reactions were reported in 18 patients. No reaction was considered to be life-threatening. The symptoms observed were: dyspnea (5), hypotension (4), pyrexia (2), injection site reaction (2), erythema (2), rash (2), arthralgia (2), chills (1), circulatory collapse (1), nausea (1), vomiting (1), tachycardia (1), myalgia (1), malaise (1), abdominal pain (1), exanthema (1), edema peripheral (1), urticaria (1), loss of consciousness (1), dizziness (1), back pain (1), headache (1).

There was no particular evolution regarding the **non-serious and listed** events. A total of 51 adverse symptoms were reported in 37 different patients. The symptoms observed were: urticaria (5), headache (5), dizziness (4), injection site extravasation (4), exanthema (3), tachycardia (3), chills (3), dyspnea (3), rash (2), flushing (2), pruritus (2), pyrexia (2), paraesthesia (2), malaise (2), hypotension (1), vomiting (1), injection site pain (1), injection site reaction (1), edema peripheral (1), arthralgia (1), myalgia (1), asthenia (1), skin discoloration (1), erythema (1).

In total, eight non-serious and anaphylactoid reactions have been reported during 6-month period out of the literature. Cumulatively, 116 anaphylactoid reactions have been reported out of the exposure of 5,123,048 patient-years to VENOFER which results in a relative prevalence of 0.0023 %.

There were 5 **serious and unlisted** adverse symptoms, involving 4 different patients. The symptoms observed were: asthma, pulmonary test decreased; abortion; respiratory failure; arthritis.

In addition, 7 patients experienced 10 **non-serious and unlisted** adverse symptoms brought to the attention of the manufacturer during the period between September 1, 2005 and February 28, 2006: edema (2), burning sensation (2), throat tightness (1), blood iron abnormal (1), arthritis (1), bone pain (1), feeling hot (1), influenza-like illness (1).

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.

Drug-Drug Interactions
Interactions with other drugs have not been established.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
The dosage of VENOFER (Iron Sucrose Injection, USP) 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 haemoglobin or hematocrit response. Patients may then continue to require therapy at the lowest dose necessary to maintain target levels of haemoglobin, hematocrit and iron storage parameters within acceptable limits (ferritin, TSAT).

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 1,000 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.

Administration

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

Dilution:

Parenteral Products:

Dose (mg Fe)	Nominal Concentration per mL	Volume of Venofer® to be Added to Diluent	Volume of Diluent
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
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
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

Dose (mg Fe)	Nominal Concentration per mL	Volume of Venofer® to be Added to Diluent	Volume of Diluent
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 **DOSAGE AND ADMINISTRATION**.

NOTE: 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.

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 **WARNINGS AND PRECAUTIONS**).

OVERDOSAGE

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

Dosages of VENOFER (Iron Sucrose Injection, USP) 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 **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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

VENOFER 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 haemoglobin 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.

Pharmacodynamics

Following intravenous administration of VENOFER, iron sucrose is dissociated by the reticuloendothelial system into iron and sucrose. In 22 hemodialysis patients on erythropoietin therapy treated with iron sucrose at 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, 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 (Vd_c) of 3.2 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 compared to healthy individuals.

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).

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 and Excretion: 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.

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

STORAGE AND STABILITY

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

VENOFER (Iron Sucrose Injection, USP) 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. NaOH 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 (Iron Sucrose Injection, USP) is available in 5 mL single dose vials, sold in boxes of 10. Each 5 mL contains 100 mg (20 mg/mL) of elemental iron as an iron (III)-hydroxide sucrose complex in water for injection.

PART II: SCIENTIFIC INFORMATION

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:

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

Molecular mass: Approximately 43,200 daltons

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.

CLINICAL TRIALS

Six clinical trials were conducted to assess the safety and efficacy of VENOFER. Five studies were conducted in the United States (516 patients) and one was conducted in South Africa (131 patients).

<u>Study A: Hemodialysis Dependent Chronic Kidney Disease (HDD-CKD)</u>

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, haemoglobin 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 haemoglobin 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 haemoglobin 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 haemoglobin and hematocrit than did patients in the historical control population. See Table 4.

Table 4 – 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 haemoglobin, 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 haemoglobin, hematocrit, and serum iron parameters was assessed.

All 23 enrolled patients were evaluated for efficacy. Statistically significant increases in mean haemoglobin (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 haemoglobin 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 haemoglobin 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 haemoglobin (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.

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 haemoglobin 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 haemoglobin ≥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 haemoglobin 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 haemoglobin 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 haemoglobin ≥1 g/dL and ferritin ≥160 ng/mL at any time during the study (p<0.0001).

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 haemoglobin 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 haemoglobin 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 haemoglobin of ≥1 g/dL during the study compared to the subjects who received erythropoietin only (33.3%) (p=0.0273).

DETAILED PHARMACOLOGY

Human

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 haemoglobin <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 haemoglobin 10.4 g/dL and mean baseline serum ferritin 50.7 ng/mL.

Pharmacokinetics:
In 12 adults with iron deficiency anemia (11 females and 1 male) 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.

Fifty eight point one (58.1)% of the sucrose was eliminated in urine in 4 h and 90.5% in 24 h. Only 4.8% of the iron was eliminated via renal excretion over the first 24 h. By 72 hours the cumulative percentage (5.02%) was essentially unchanged. The urinary excretion of sucrose and iron was comparable to the results obtained in healthy adults following the administration of a 100 mg dose.

Eligibility for this study included iron deficient (ferritin < 20 ng/L and no other causes of anemia) patients with a haemoglobin between 9.0 to 13.5 g/dL in males and 9.0 to 12.5 g/dL in females, with a BMI within 20% of ideal. The mean patient age was 31 years (range 18-55), mean weight 66.6 kg (range of 55-96 kg), mean BMI 24.4 (range 19.8-29) kg/m^2, mean haemoglobin 11.1 g/dL and mean baseline serum ferritin 3.7 ng/mL. The ferritin level was obtained on Day 1, 2 and 3 following dosing and peaked on Day 2 with a value of 293 (SD 81) ng/mL.

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.

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.

Repeat-Dose Toxicity
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, haematological 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 pigmentosis beginning about 3 years after iron administration.

Mutagenicity and 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.

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

Reproduction
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.

REFERENCES [

1. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease, 2000. *Am J Kidney Dis* 37: S182-S238.

2. Charytan C, Levin A, Al-Saloum M, et al. Efficacy and Safety of Iron Sucrose for Iron Deficiency in Patients with Dialysis-Associated Anemia: North American Clinical Trial. *Am J Kidney Dis* 37 (2): 300-307, 2001.

3. Van Wyck DB, Cavallo G, Spinowitz BS, et al. Safety and Efficacy of Iron Sucrose in Patients Sensitive to Iron Dextran: North American Clinical Trial. *Am J Kidney Dis* 36 (1): 88-97, 2000.

4. Danielson BG et al. Pharmacokinetics of iron (III)-hydroxide sucrose complex after a single intravenous dose in healthy volunteers. *Arzneim-Forsch/Drug Res* 46(I); 6: 615-621, 1996.

5. Beshara S, Lundqvist H, Sundin J, et al. Kinetic analysis of ^{52}FE-labeled iron (III) hydroxide-sucrose complex following bolus administration using positron emission tomography. *Brit J of Haematology* 104: 288-295, 1999.

6. Pribilla W. Animal experiments investigating the iron transfer between mother and fetus after the intravenous administration of iron. *Acta Haemat* 12: 371-384, 1954.

7. Wöhler F. The iron supply to the fetus. Reprinted from *Archiv für Kinderheilkunde* 155 (3), 1957.

PART III: CONSUMER INFORMATION

VENOFER
Iron Sucrose Injection, USP

This leaflet is part III of a three-part "Product Monograph" published when VENOFER was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about VENOFER. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
VENOFER is used in the treatment of iron deficiency anemia in dialysis dependent or non-dialysis-dependent chronic kidney disease patients.

What it does:
VENOFER is used to replenish body iron stores in dialysis dependent or non-dialysis-dependent chronic kidney disease patients. Iron deficiency may be caused by blood loss during dialysis, increased production of red blood cells secondary to erythropoietin use, and insufficient absorption of iron from the gastrointestinal tract. Iron is needed to make haemoglobin, which allows red blood cells to carry oxygen throughout the body. Most dialysis patients require intravenous iron to maintain sufficient iron stores.

When it should not be used:
The use of VENOFER is contraindicated in patients with too much iron (iron overload) in their body, patients with known hypersensitivity (allergy or sensitivity) to VENOFER, and patients with anemia not caused by iron deficiency.

What the medicinal ingredient is:
Iron sucrose

What the important nonmedicinal ingredients are:
For a full listing of nonmedicinal ingredients see Part I of the Product Monograph.

What dosage forms it comes in:
5 mL Single Dose Vials, 20 mg elemental iron/mL

WARNINGS AND PRECAUTIONS

BEFORE you use VENOFER talk to your doctor or pharmacist if:

- You are hypersensitive to injectable iron products;
- You have symptoms of iron overload (see **Overdose**);
- You are pregnant or planning to become pregnant.
- You are breastfeeding or planning to breastfeed. Animal studies show that Venofer is excreted in breast milk.

Low blood pressure has been reported frequently in hemodialysis patients receiving intravenous iron.

Only a qualified doctor or other healthcare professional should administer VENOFER. VENOFER is not intended for administration by patient.

The safety and effectiveness of VENOFER in pediatric patients has not been established.

Caution should be used when administering VENOFER to elderly patients, usually starting with the lowest dose.

INTERACTIONS WITH THIS MEDICATION

Drug interactions involving VENOFER have not been studied. Oral iron should not be administered together with other injectable iron preparations. Like other injectable iron preparations, VENOFER may reduce the absorption of oral iron preparations.

PROPER USE OF THIS MEDICATION

Usual dose:
Only a qualified doctor or other healthcare professional should administer VENOFER. VENOFER is not intended for administration by patient.

Recommended Adult Dosage:

The dose of VENOFER is expressed in terms of mg of elemental iron.

Chronic Kidney Disease Patients not on Dialysis: VENOFER is administered as a total cumulative dose of 1000 mg over a 14 day period, either as a 200 mg slow intravenous injection on 5 different occasions within the 14 day period, or as an infusion of 500 mg of VENOFER over a period of 4 hours on day 1 and day 14. Patients weighing less than 70 kg may require longer infusion times.

Hemodialysis Patients: VENOFER is administered as a 100 mg slow intravenous injection or as an infusion of 100 mg per consecutive hemodialysis session for a total cumulative dose of 1000 mg.

Peritoneal Dialysis Patients: 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.

Overdose:

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

Symptoms associated with overdosage or infusing VENOFER too rapidly include low blood pressure, headache, vomiting, nausea, dizziness, joint aches, a burning, pricking or tingling feeling, abdominal and muscle pain, swelling, and cardiovascular collapse

(shock).

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Common side effects that may occur include: nausea, dizziness, headache, vomiting, diarrhea, abdominal pain, fever, chest pain, muscle cramps (especially leg cramps). If these become bothersome, consult your doctor.

Very rare cases of severe, sometimes life-threatening allergic reactions (loss of consciousness, collapse, difficulty breathing or convulsions) and cases of severe low blood pressure (hypotension) have been reported with the use of VENOFER. Only a qualified doctor or other healthcare professional should administer VENOFER. VENOFER is not intended for administration by patient.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Serious Side Effects	**Severe allergic reactions, sometimes life threatening with symptoms such as difficulty breathing, convulsion, collapse, itching, rash.**		✔	
	Low blood pressure, with symptoms such as fainting, weakness.		✔	

This is not a complete list of side effects. For any unexpected effects while taking VENOFER, contact your doctor or pharmacist.

HOW TO STORE IT

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

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

Manufactured by:

Luitpold Pharmaceuticals, Inc.
One Luitpold Drive, P.O Box 9001
Shirley, New York 11967

Distributed by:
Bellco Health Care Inc.
2900 Argentia Road, Unit 10
Mississauga, Ontario
Canada L5N 7X9

This document, plus the full product monograph prepared for health professionals, can be found at:
http://www.luitpold.com or www.americanregent.com
or by contacting the sponsor, Luitpold Pharmaceuticals, Inc., at:
1-800-645-1706

This leaflet was prepared by Luitpold Pharmaceuticals, Inc..

Last revised: January 15, 2013