

U.S. Hospitals Resume Care for Injured Haitians

BY ROBERT FINN

Medical evacuations of patients critically injured in Haiti's devastating earthquake to hospitals in the United States resumed on Feb. 1, following a 5-day interruption.

The exact cause of the interruption appears to be under dispute. According to published reports, some sources said the issue involved how hospitals would

be reimbursed for caring for these patients. Other sources cited a lack of capacity at hospitals in Florida, where most of the patients had been sent.

White House spokesman Tommy Vitor said that logistical problems had caused the interruption. He pointed to difficulties in locating appropriate medical facilities that were close to airports capable of handling large military transport planes.

Whatever the cause, the flights resumed the day after Kathleen Sebelius, Secretary of the Department of Health and Human Services, activated components of the National Disaster Medical System (NDMS). With this announcement, hospitals that are part of the NDMS could be assured that the federal government would pay them for the patients' care at 110% of the Medicare reimbursement rate.

The flights were halted on Jan. 27, shortly after Florida Governor Charlie Crist wrote a letter to Secretary Sebelius stating that medical facilities in Florida were "quickly reaching saturation, especially in the area of high-level trauma care."

In that letter, Governor Crist also pointed to a "lack of coordination by federal authorities" overseeing the evacuations. He noted that 436 patients had been admitted to Florida hospitals, with more than 90% suffering from multiple traumas.

"Recently, we learned that federal planning is underway to move between

With the National Disaster Medical System activated, 'evacuations have only been used in limited instances where patients had medical needs that could not be met in Haiti.'

30-50 critically ill patients per day for an indefinite period of time," Governor Crist's letter continued. "Florida does not have the capacity to support such an operation."

The U.S. Agency for International Development (USAID) is coordinating the government's response to the earthquake. In a statement announcing the activation of the NDMS, USAID administrator Dr. Rajiv Shah stated, "Medical evacuations have only been used in limited instances where patients had medical needs that could not be met in Haiti. We are committed to working with the Haitian people and the Government of Haiti to create long-term care facilities in-country. Continued medical assistance is critical to these efforts."

In a Feb. 1 statement responding to the NDMS activation, Governor Crist said that "Florida is grateful to our federal partners for taking steps to activate the National Disaster Medical System. The quick response to my letter last week to Secretary Sebelius will ensure that critically injured survivors of the Haiti earthquake will continue to receive the medical care they so desperately need."

Governor Crist noted that Florida had committed to welcoming 19,000 people from Haiti including, as of that date, 526 patients who were receiving critical medical care.

"Florida's hospitals, doctors, nurses and medical teams are at the forefront of caring for survivors, both here in Florida and in Haiti," he continued. "For their tireless efforts, I commend their dedication to promptly and compassionately serving those in need."

The day following the NDMS announcement, medical evacuation flights resumed, arriving in Tampa and Atlanta. Hospitals in New York, Boston, Philadelphia, and Lyons, N.J., were also alerted that patients might be sent to those facilities.

Venoferr[®] iron sucrose injection, USP

Brief Summary (See Package Insert For Full Prescribing Information)

Therapeutic Class: Hematinic
CLINICAL INDICATIONS AND USAGE

Venoferr (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

CONTRAINDICATIONS

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

WARNINGS

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

PRECAUTIONS

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

Hypersensitivity Reactions: Serious hypersensitivity reactions have been reported in patients receiving Venoferr. No life-threatening hypersensitivity reactions were observed in the clinical studies. Several cases of mild or moderate hypersensitivity reactions were observed in these studies. There are post-marketing spontaneous reports of life-threatening hypersensitivity reactions in patients receiving Venoferr. See ADVERSE REACTIONS.

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 and peritoneal dialysis dependent chronic kidney disease patients receiving intravenous iron. Hypotension following administration of Venoferr may be related to rate of administration and total dose administered. Caution should be taken to administer Venoferr according to recommended guidelines. See DOSAGE AND ADMINISTRATION.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

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

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

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

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

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

Pediatric Use: Safety and effectiveness of Venoferr in pediatric patients have not been established. In a country where Venoferr 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 Venoferr, several other medications and erythropoietin. Necrotizing enterocolitis may be a complication of prematurity in very low birth weight infants. No causal relationship to Venoferr or any other drugs could be established.

Geriatric Use: The five pivotal clinical trials did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. No overall differences in safety were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Adverse Events observed in all treated populations

The frequency of adverse events associated with the use of Venoferr has been documented in six randomized clinical trials involving 231 hemodialysis dependent, 139 non-dialysis dependent and 75 peritoneal dialysis dependent-CKD patients; and in two post-marketing safety studies involving 1,051 hemodialysis dependent-CKD patients for a total of 1,496 patients. In addition, over 2,000 patients treated with Venoferr have been reported in the medical literature.

Treatment-emergent adverse events reported by ≥ 2% of treated patients with NDD-CKD in the randomized clinical trials, whether or not related to Venoferr administration, are listed by indication in Table 2. Treatment-emergent adverse events reported in ≥ 2% of patients by dose group are shown in Table 3.

Table 2. Most Common Treatment-Emergent Adverse Events Reported in ≥ 2% of Patients with NDD-CKD by Clinical Indication (Multidose Safety Population)

Adverse Events (Preferred Term)	NDD-CKD	
	Venoferr (N=139) %	Oral Iron (N=139) %
Subjects with any adverse event	76.3	73.4
Ear and Labyrinth Disorders		
Ear Pain	2.2	0.7
Eye Disorders		
Conjunctivitis	0	0
Gastrointestinal Disorders		
Abdominal pain NOS*	1.4	2.9
Constipation	4.3	12.9
Diarrhea NOS	7.2	10.1
Dysgeusia	7.9	0
Nausea	8.6	12.2
Vomiting NOS	5.0	8.6
General Disorders and Administration Site Conditions		
Asthenia	0.7	2.2
Chest pain	1.4	0
Edema NOS	6.5	6.5
Fatigue	3.6	5.8
Feeling abnormal	0	0
Infusion site burning	3.6	0
Injection site extravasation	2.2	0
Injection site pain	2.2	0
Peripheral edema	7.2	5.0
Pyrexia	0.7	0.7
Infections and Infestations		
Catheter site infection	0	0
Nasopharyngitis	0.7	2.2
Peritoneal infection	0	0
Sinusitis NOS	0.7	0.7
Upper respiratory tract infection NOS	0.7	1.4
Urinary tract infection NOS	0.7	5.0
Injury, Poisoning and Procedural Complications		
Graft complication	1.4	0
Investigations		
Cardiac murmur NOS	2.2	2.2
Fecal occult blood positive	1.4	3.6
Metabolism and Nutrition Disorders		
Fluid overload	1.4	0.7
Gout	2.9	1.4
Hyperglycemia NOS	2.9	0
Hypoglycemia NOS	0.7	0.7
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	1.4	2.2
Arthritis NOS	0	0

Table 3. Most Common Treatment-Emergent Adverse Events Reported in ≥ 2% of Patients with NDD-CKD by Dose Group (Multidose Safety Population)

Adverse Events (Preferred Term)	NDD-CKD	
	200 mg (N=109) %	500 mg (N=30) %
Subjects with any adverse event	75.2	80.0
Ear and Labyrinth Disorders		
Ear Pain	0.9	6.7
Eye Disorders		
Conjunctivitis	0	0
Gastrointestinal Disorders		
Abdominal pain NOS*	1.8	0
Constipation	3.7	6.7
Diarrhea NOS	6.4	10.0
Dysgeusia	9.2	3.3
Nausea	9.2	6.7
Vomiting NOS	5.5	3.3
General Disorders and Administration Site Conditions		
Asthenia	0.9	0
Chest pain	0.9	3.3
Edema NOS	7.3	3.3
Fatigue	4.6	0
Feeling abnormal	0	0
Infusion site burning	3.7	3.3
Injection site pain	2.8	0
Peripheral edema	5.5	13.3
Pyrexia	0.9	0
Infections and Infestations		
Catheter site infection	0	0
Nasopharyngitis	0.9	0
Peritoneal infection	0	0
Sinusitis NOS	0	3.3
Upper respiratory tract infection NOS	0.9	0
Injury, Poisoning and Procedural Complications		
Graft complication	1.8	0
Investigations		
Cardiac murmur NOS	2.8	0
Fecal occult blood positive	1.8	0
Metabolism and Nutrition Disorders		
Fluid overload	1.8	0
Gout	1.8	6.7
Hyperglycemia NOS	3.7	0
Hypoglycemia NOS	0.9	0
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	0.9	3.3
Back pain	1.8	3.3
Muscle cramp	0	3.3
Myalgia	2.8	6.7

(Table 2 continued)

Adverse Events (Preferred Term)	NDD-CKD	
	Venoferr (N=139) %	Oral Iron (N=139) %
Musculoskeletal and Connective Tissue Disorders		
Back pain	2.2	3.6
Muscle cramp	0.7	0.7
Myalgia	3.6	0
Pain in extremity	4.3	0
Nervous System Disorders		
Dizziness	6.5	1.4
Headache	2.9	0.7
Hypoesthesia	0.7	0.7
Respiratory, Thoracic and Mediastinal Disorders		
Cough	2.2	0.7
Dyspnea	3.6	0.7
Dyspnea exacerbated	2.2	0.7
Nasal congestion	1.4	2.2
Pharyngitis	0	0
Rhinitis allergic NOS	0.7	2.2
Skin and Subcutaneous Tissue Disorders		
Pruritus	2.2	4.3
Rash NOS	1.4	2.2
Vascular Disorders		
Hypertension NOS	6.5	4.3
Hypotension NOS	2.2	0.7

*NOS=Not otherwise specified

Drug related adverse events reported by ≥ 2% of Venoferr (iron sucrose injection, USP) treated patients are shown by dose group in Table 4.

Table 4. Most Common Adverse Events Related to Study Drug Reported in ≥ 2% of Patients with NDD-CKD by Dose Group (Multidose Safety Population)

Adverse Events (Preferred Term)	NDD-CKD	
	200 mg (N=109) %	500 mg (N=30) %
Subjects with any adverse event	23.9	20.0
Gastrointestinal Disorders		
Diarrhea NOS	0	0
Dysgeusia	7.3	3.3
Nausea	2.8	0
General Disorders and Administration Site Conditions		
Infusion site burning	3.7	0
Injection site pain	2.8	0
Peripheral edema	1.8	6.7
Nervous System Disorders		
Dizziness	2.8	6.7
Headache	2.8	0
Vascular Disorders		
Hypertension NOS	0	6.7

*NOS=Not otherwise specified

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

In the pivotal study of 182 NDD-CKD patients, 91 were exposed to Venoferr. Adverse events, whether or not related to Venoferr, reported by ≥ 5% of the Venoferr 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 Venoferr patient). Two patients experienced possible hypersensitivity/allergic reactions (local edema/hypertension) 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 Venoferr group), three Venoferr patients had events that were considered drug-related (hypotension, dyspnea and nausea).

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 Venoferr at a dose of 500 mg. Constipation occurred in 1 patient treated with Venoferr at a dose of 500 mg.

The post-marketing spontaneous reporting system includes reports of patients who experienced serious or life-threatening reactions (anaphylactic shock, loss of consciousness or collapse, bronchospasm with dyspnea, or convulsion) associated with Venoferr administration.

OVERDOSAGE

Dosages of Venoferr (iron sucrose injection, USP) in excess of iron needs may lead to accumulation of iron in storage sites leading to hemosiderosis. Periodic monitoring of iron parameters such as serum ferritin and transferrin saturation may assist in recognizing iron accumulation. Venoferr should not be administered to patients with iron overload and should be discontinued when serum ferritin levels equal or exceed established guidelines [1]. Particular caution should be exercised to avoid iron overload where anemia unresponsive to treatment has been incorrectly diagnosed as iron deficiency anemia.

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

Preclinical Data:

Single IV doses of Venoferr at 150 mg iron/kg in mice (about 3 times the recommended maximum human dose on a body surface area basis) and 100 mg iron/kg in rats (about 8 times the recommended maximum human dose on a body surface area basis) were lethal. The symptoms of acute toxicity were sedation, hypocoactivity, pale eyes, and bleeding in the gastrointestinal tract and lungs.

DOSAGE AND ADMINISTRATION

The dosage of Venoferr is expressed in terms of mg of elemental iron. Each mL contains 20 mg of elemental iron. Most CKD patients will require a minimum cumulative repletion dose of 1,000 mg of elemental iron, administered over sequential sessions, to achieve a favorable hemoglobin response and to replenish iron stores (ferritin, TSAT).

Administration: Venoferr must only be administered intravenously either by slow injection or by infusion.

Recommended Adult Dosage:

Non-Dialysis Dependent Chronic Kidney Disease Patients (NDD-CKD): Venoferr 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 Venoferr diluted in a maximum of 250 mL of 0.9% NaCl over a period of 2.5-4 hours on day 1 and day 14; hypotension occurred in 2 of 30 patients treated. See CLINICAL TRIALS, Study D: Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD) Patients and ADVERSE REACTIONS, Adverse Events Observed in Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD) Patients sections.

HOW SUPPLIED

Venoferr is supplied in 5 mL and 10 mL single dose vials. Each 5 mL vial contains 100 mg elemental iron (20 mg/mL) and each 10 mL vial contains 200 mg elemental iron (20 mg/mL). Contains no preservatives. Store in original carton at 25°C (77°F). Excursions permitted to 15°-30°C (59°-86°F). See the USP controlled room temperature. Do not freeze.

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

Rx Only

REFERENCE: [1] National Kidney Foundation. KDQOL Clinical Practice Guidelines for Anemia of Chronic Kidney Disease, 2000. *Am J Kidney Dis*. 37:S182-S238, (suppl 1) 2001.



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