

HHS Funds New Research to Fight Infections

BY JANE ANDERSON

The Department of Health and Human Services has awarded \$17 million to fund research projects aimed at reducing central line-associated bloodstream infections and other hospital-acquired infections, including methicillin-resistant *Staphylococcus aureus*.

Nearly half of the funds will go toward financing a national expansion of the

Keystone Project, which uses a checklist of evidence-based safety practices, staff training, careful measurement of infection rates, and teamwork-building tools for hospital staff to reduce the rate of central line-associated bloodstream infections (CLABSIs), according to the HHS.

The program, which has been implemented in more than 100 Michigan intensive care units, has saved more than 1,800 lives, more than \$271 million in

health care costs, and more than 140,700 excess hospital stay days in that state between 2004 and 2009, according to the Michigan Health and Hospital Association in Lansing.

In addition, data indicate that the CLABSI rates of hospitals participating in the Keystone program were consistently lower than the national average, the hospital association said in an October report.

Last year, the Agency for Healthcare Research and Quality (AHRQ) funded an expansion of the Keystone Project to 10 states. Now, with additional funding from the AHRQ and a private foundation, it is operating in all 50 states, the HHS said. The additional \$8 million from the HHS will allow the program to expand to more hospitals, to extend to other settings in addition to intensive care units, and to broaden the focus to address other types of infections, the HHS said.

Dr. Thomas W. Barrett, a hospitalist at the Portland (Ore.) VA Medical Center, said in an interview that this type of implementation research is difficult to conduct because there are so many potentially confounding variables.

"This is a great step forward—it's very important for patient safety and patient care," Dr. Barrett said. "It's encouraging



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DR. BARRETT

to see AHRQ take a great step in the right direction. I hope that since AHRQ is funding this, the level of rigor in the research will continue to improve."

To spend the remaining \$9 million of the \$17 million in new funding, the AHRQ said it collaborated with the Centers for Disease Control and Prevention to identify projects.

The projects chosen will focus on reducing *Clostridium difficile* infections through a regional hospital collaborative, reducing the overuse of antibiotics by primary care physicians treating patients in ambulatory and long-term care settings, evaluating two ways to eliminate MRSA in ICUs, and improving the measurement of the risk of infections after surgery.

Additional projects will attempt to identify rates of hospital-acquired infections, to reduce infections caused by *Klebsiella pneumoniae* carbapenemase-producing organisms by applying recently developed recommendations from the CDC's Healthcare Infection Control Practices Advisory Committee, to standardize antibiotic use in long-term care settings, and to implement teamwork principles for frontline health care providers, the AHRQ said.

VERBATIM

'We thought we had a plan in place,' but 'we were operating in silos.'

Lorraine Quatrone, medical administrator, on preparedness for working without computers or phones at Children's Specialized Hospital, New Brunswick, N.J., p. 19

Venofor[®]

iron sucrose injection, USP

Brief Summary (See Package Insert For Full Prescribing Information)

Therapeutic Class: Hematinic

CLINICAL INDICATIONS AND USAGE

Venofor[®] (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 Venofor[®] is contraindicated in patients with evidence of iron overload, in patients with known hypersensitivity to Venofor[®] 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 tissue iron can be hazardous, caution should be exercised to withhold iron administration in the presence of evidence of tissue iron overload. Patients receiving Venofor[®] require periodic monitoring of hematologic and hematimetric parameters (hemoglobin, hematocrit, serum ferritin and transferrin saturation). Iron therapy should be withheld in patients with evidence of iron overload. Transferrin saturation values increase rapidly after IV administration of iron sucrose; thus, serum iron values may be reliably obtained 48 hours after IV dosing. See DOSAGE AND ADMINISTRATION and OVERDOSAGE.

Hypersensitivity Reactions: Serious hypersensitivity reactions have been reported in patients receiving Venofor[®]. 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 Venofor. 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 Venofor[®] may be related to rate of administration and total dose administered. Caution should be taken to administer Venofor[®] 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 Venofor[®].

Venofor[®] 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.

Venofor[®] 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 Venofor[®]. 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: Venofor[®] 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 Venofor[®] is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of Venofor[®] in pediatric patients have not been established. In a country where Venofor[®] 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 Venofor[®], several other medications and erythropoietin. Necrotizing enterocolitis may be a complication of prematurity in very low birth weight infants. No causal relationship to Venofor[®] 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 Venofor[®] 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 Venofor[®] 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 Venofor[®] administration, are listed by indication in Table 2.

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	
	Venofor [®] (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	
	Venofor [®] (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

(Table 3 continued)

Adverse Events (Preferred Term)	NDD-CKD	
	200 mg (N=109) %	500 mg (N=30) %
Musculoskeletal and Connective Tissue Disorders		
Pain in extremity	4.6	3.3
Nervous System Disorders		
Dizziness	5.5	10.0
Headache	3.7	0
Respiratory, Thoracic and Mediastinal Disorders		
Cough	0.9	6.7
Dyspnea	1.8	10.0
Pharyngitis	0	0
Skin and Subcutaneous Tissue Disorders		
Pruritus	0.9	6.7
Vascular Disorders		
Hypertension NOS	6.4	6.7
Hypotension NOS	0.9	6.7

*NOS=Not otherwise specified

Drug related adverse events reported by ≥ 2% of Venofor[®] (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		
Hypotension 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 Venofor[®]. Adverse events, whether or not related to Venofor[®], reported by ≥ 5% of the Venofor[®] 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 hypotension (5.5%). One serious related adverse reaction was reported (hypotension and shortness of breath) not requiring hospitalization in a Venofor[®] 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 Venofor[®] group), three Venofor[®] 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 Venofor[®] 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 Venofor[®] administration.

OVERDOSAGE

Dosages of Venofor[®] (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. Venofor[®] 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 Venofor[®] 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, hyaluronidase, and/or antihistamines. Infusing the solution as recommended or at a slower rate may also alleviate symptoms.

Preclinical Data:

Single IV doses of Venofor[®] 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 Venofor[®] 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 replacement dose of 1,000 mg of elemental iron, administered over sequential sessions, to achieve a favorable hemoglobin response and to replenish iron stores (ferritin, TSA).

Administration: Venofor[®] must only be administered intravenously either by slow injection or by infusion.

Recommended Adult Dosage:

Non-Dialysis Dependent Chronic Kidney Disease Patients (NDD-CKD): Venofor[®] is administered as a total cumulative dose of 1,000 mg over a 14 day period as a 200 mg slow IV injection diluted 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 Venofor[®] 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. 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

Venofor[®] 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
NDC-0517-2340-10 100 mg/5 mL Single Dose Vial Packages of 10
NDC-0517-2340-25 100 mg/5 mL Single Dose Vial Packages of 25

Rx Only

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

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