Feridex I.V.®
(ferumoxides injectable solution)

REV 08

DESCRIPTION

Feridex I.V.® (ferumoxides injectable solution) is a sterile aqueous colloid of superparamagnetic iron oxide associated with dextran for intravenous (i.v.) administration as a magnetic resonance imaging contrast media. Chemically, ferumoxides is a non-stoichiometric magnetite, of average formula $FeO_{1.44}$. Each milliliter of Feridex I.V. contains 11.2 milligrams of iron and 61.3 milligrams of mannitol at a pH of 5 to 9. The formulation also contains dextran (5.6–9.1 mg/mL) and citrate (0.25–0.53 mg/mL). The osmolality is approximately 340 mOsm/kg; specific gravity is 1.04. Feridex I.V. is a black to reddish-brown aqueous colloid.

CLINICAL PHARMACOLOGY

General: Feridex I.V. is an intravenously injected colloidal superparamagnetic iron oxide associated with dextran. It is a magnetic resonance imaging (MRI) contrast agent and is taken up by cells of the reticuloendothelial system (RES).

Pharmacokinetics:

Three healthy, adult male volunteers received a dose of Feridex I.V. 0.56 mg of Fe/kg (diluted in 100 mL of 5% dextrose and intravenously infused over 30 minutes). In these subjects, the mean ± SD peak serum iron concentration was 5.5 ± 0.6 µg/mL, elimination half-life was 2.4 ± 0.2 hours and total clearance 28.5 ± 1.6 mL/min. Feridex I.V. was completely cleared from the blood by 25 hours after administration. Less than 2% of the drug was excreted in the urine, as expected for iron.

At 24 hours, serum iron increased and the percent saturation of iron binding capacity decreased in a dose-dependent fashion. By 7 days, serum iron returned to pre-administration levels, and serum ferritin increased. These results are consistent with the iron in Feridex I.V. entering the usual iron metabolism cycle. Animal pharmacokinetics studies were consistent with these results in humans.

Imaging studies in rats showed a large decrease in liver signal intensity for the first 24 hours after dosing, followed by a gradual return to normal over 7 days. Radiotracer studies in rats were consistent with the iron in Feridex I.V. becoming part of the body iron pool. Histological studies in rats showed that the iron was in the RES and that it disappeared from the RES over 7 to 14 days with all evidence of iron gone by 14–28 days.

In human clinical studies, there was no difference in loss of signal intensity on images obtained between 0–3.5 hours after infusion. Loss of signal intensity decreased at 1 and 2 days.

Metabolism: The iron in Feridex I.V. enters the normal body iron metabolism cycle as evidenced by transient increases in serum iron values one day after administration and increase in serum ferritin values 7 days after administration. The amount of iron contained in a single dose is 39 mg for a 70 kg individual. This is less than 1/5 the amount of iron contained in one unit of whole blood.

Special Populations:

Geriatric/Pediatric: Pharmacokinetics in these populations were not studied. Patients enrolled in clinical trials were between 11 and 89 years old.

Gender: Women showed a higher pre-contrast signal intensity and hence a larger decrease in liver signal intensity in images. This is consistent with a lower baseline iron in women.

Race: Differences due to race were not noted.

Renal Insufficiency: Feridex I.V. is not renally cleared; no studies were performed in patients with renal insufficiency.

Hepatic Insufficiency: Patients with cirrhosis had less of a decrease in liver signal intensity than other patients with known or suspected liver lesions. Patients with cirrhosis also had a higher incidence of back pain. (**See ADVERSE REACTIONS section.**)

Hemochromatosis: Individuals with iron overload were not studied. Feridex I.V. contains iron. Literature reports suggested that Feridex I.V. will not add information to their MRI evaluations, since iron overload causes loss in liver signal intensity.

Drug-Drug Interactions: In rats, the simultaneous administration of heparin was found to prolong the half-life of Feridex I.V. in the blood. The effects of Feridex I.V. administration on heparin anticoagulation are not known.

Pharmacodynamics: Feridex I.V. shortens the relaxation times for nearby hydrogen atoms and reduces signal intensity in normal tissues. This results in signal loss (image darkening) on mid T1/T2 or strongly T2-weighted images. Tissues with decreased RES function (e.g., metastases, primary liver cancer, cysts and various benign tumors, adenomas, and hyperplasia) retain their native signal intensity, so the contrast between normal and abnormal tissue is increased.

CLINICAL TRIALS

Two clinical studies evaluated a total of 211 patients, (107 men and 104 women, 22–83 years of age) with a variety of known or suspected liver lesions. Of these patients, efficacy evaluations were completed on 96 patients in Study A, and 112 patients in Study B. At baseline, patients had a CECT (contrast enhanced computerized tomography) scan with any iodinated contrast agent and a noncontrast MRI (magnetic resonance imaging) within 24 hours before Feridex I.V. administration. Feridex I.V. (0.56 mg/kg) was administered intravenously over 30 minutes. Images were acquired up to 3.5 hours after the end of the infusion. The CECT, unenhanced MRI, and Feridex I.V. enhanced MRI images were read blindly (i.e., by radiologists who were not told of the patient's medical history or the presence of image contrast enhancing drugs). Results from blindly read images were compared to the final clinical diagnosis. The final clinical diagnoses were confirmed with histopathologic, surgical, or biopsy findings in 86 (41%) of patients. MRI scans were evaluated for the quantitative analysis of signal intensity in liver lesion(s), and by blinded evaluations of the resulting images for changes in number and location of lesions, delineation of lesion margins, presence or absence of lesions, and characterization of lesions.

Based upon these two studies, Feridex I.V. reduced the signal intensity of normal liver on T2 weighted pulse sequences to improve MRI contrast. Contrast to noise ratios were increased on T2 images and decreased on T1 images. Image interpretations for contrast enhancement, the number of lesions identified, and the sensitivity and specificity of the determination of whether an abnormal lesion was present are shown in the following table. The mean number of lesions seen before and after Feridex I.V. were comparable. The majority of new lesions (86%) were 0.5 cm–1.0 cm in size, but other lesions were seen that were <0.5 cm or >1.0 cm.

IMAGE INTERPRETATION RESULTS AFTER UNENHANCED MRI, CECT AND FERIDEX I.V. ENHANCED MRI IN TWO CLINICAL STUDIES OF PATIENTS WITH KNOWN OR SUSPECTED LIVER LESIONS**

Outcome Measure	Control Comparisons	Study A (N = 96)	Study B (N=112)
Contrast between normal and abnormal liver tissue seen on MRI	MRI Contrast Better with Feridex I.V.	84%	86%
	MRI Contrast Same with Feridex I.V.	13%	12%
	MRI Contrast Worse with Feridex I.V.	3%	2%
		(p<0.01)	(p<0.01)
Number of Patients with Lesions Seen on MRI	Patients with: More before Feridex I.V.	13%	21%
	Same before and after Feridex I.V.	62%	51%
	More After Feridex I.V	25%	28%
Number of liver lesions seen on MRI (Mean ± SD)	MRI before Feridex I.V.	7.3 ± 15.9	6.7 ± 14.8
	after Feridex I.V.	6.7 ± 10.4	7.3 ± 15.5
		(p=n.s.)	(p=n.s.)
Sensitivity/specificity for the detection of abnormal liver lesions	MRI before Feridex I.V. vs. Final diagnosis:* Sensitivity	91%	92%
	Specificity	71%	77%
	MRI after Feridex I.V. vs. Final diagnosis:*		
	Sensitivity	95%	92%
	Specificity	76%	85%
	CECT vs. Final diagnosis:*		
	Sensitivity	96%	98%
	Specificity	67%	58%

* Final diagnosis: e.g., by biopsy, surgical resection, autopsy, MRI procedures other than with Feridex I.V., CECT, ultrasound, or other clinical information.

** MRI (magnetic resonance image), CECT (contrast enhanced computerized tomography)

In various types of liver lesions, Feridex I.V. caused a smaller decrease in the signal intensity (59%–105% of the unenhanced) than in the surrounding liver (28%–41% of the unenhanced). The signal intensity changes are not characterized sufficiently to support distinguishing between types of lesions or diseases. Whether patients with cirrhosis have similar changes in signal intensity is not known.

PERCENT DECREASE IN MRI SIGNAL INTENSITY (SI) ON T2 IMAGES AFTER FERIDEX I.V.

Disease State	Surrounding Liver N	Surrounding Liver % decrease in SI after Feridex I.V.	Lesions in Question N	Lesions in Question % decrease in SI after Feridex I.V.
Patients with benign, malignant, hepatocellular and non-hepatocellular lesions (excluding cirrhosis)	162	59–72%	153	0–41%

Imaging of the spleen by Feridex I.V. has not been adequately studied.

INDICATION AND USAGE

Feridex I.V. is indicated for I.V. administration as an adjunct to MRI (in adult patients) to enhance the T2 weighted images used in the detection and evaluation of lesions of the liver that are associated with an alteration in the RES.

CONTRAINDICATIONS

Feridex I.V. is contraindicated in patients with known allergic or hypersensitivity reactions to parenteral iron, parenteral dextran, parenteral iron-dextran, or parenteral iron-polysaccharide preparations.

WARNINGS

Anaphylactic-like reactions and hypotension have been noted in some patients receiving Feridex I.V., other iron and dextran containing formulations, or radiographic contrast media. In clinical trials, anaphylactic and allergic adverse events occurred in 11/2240 (0.5%) of the patients who received Feridex I.V. These events include dyspnea, other respiratory symptoms, angioedema, generalized urticaria, and hypotension; and required treatment.

Acute severe back, leg or groin pain occurred in some patients. In clinical trials, 55/2240 (2.5%) of the patients experienced pain that was severe enough to cause interruption or discontinuation of the infusion. In most patients, the symptoms developed within 1 to 15 minutes (up to 45 minutes). Some patients required treatment with corticosteroids, intravenous fluids or muscle relaxants. Pain may occur alone or with other symptoms such as hypotension and dyspnea. Patients with both pain and allergic symptoms received treatment with a combination of medications directed toward each event. (**See ADVERSE REACTIONS section.**)

Patients with autoimmune disease have not been studied with Feridex I.V., but have been reported in published literature to have a high rate of adverse reactions to injectable iron formulations.

If hypersensitivity, or moderate to severe pain occurs, the injection should be stopped, and symptomatic treatment should be given.

A fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognizing and treating anaphylactic or anaphylactoid reactions should be available.

PRECAUTIONS

GENERAL: THE DECISION TO USE CONTRAST ENHANCEMENT SHOULD INCLUDE A CONSIDERATION OF THE RISK OF THE DRUG, THE RISK OF THE PROCEDURE, THE EXPECTED BENEFIT OF THE IMAGE AND THE PATIENT'S UNDERLYING DISORDER. THE DECISION TO USE FERIDEX I.V. SHOULD BE BASED UPON CAREFUL EVALUATION OF CLINICAL DATA, OTHER RADIOLOGIC DATA, AND THE RESULTS OF UNENHANCED MRI.

Patients receiving contrast agents and especially those who are medically unstable must be closely supervised. Diagnostic procedures which involve the use of any contrast agent should be carried out under the direction of personnel with the prerequisite training and with a thorough knowledge of the particular procedure to be performed.

After parenteral administration of a contrast agent, competent personnel, a fully equipped emergency cart or equivalent, and emergency facilities should be available for at least 60 to 120 minutes.

Immunologic Reactions:

The possibility of a reaction including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions should always be considered. Increased risk is associated with a known sensitivity to iron or dextran, history of previous reaction to a radiographic contrast agent, known allergies, other hypersensitivities, and underlying immune disorders, autoimmunity or immunodeficiencies that predispose to specific or non specific mediator release.

Skin testing cannot be relied upon to predict severe reactions and skin testing may itself be hazardous to the patient. A thorough medical history with emphasis on allergy and hypersensitivity, immune, autoimmune and immunodeficiency disorders, and prior receipt of and response to the injection of any contrast agent, may be more accurate than pretesting in predicting potential adverse reactions.

Feridex I.V., which contains iron, should be used with caution in patients with disorders associated with iron over load (e.g., hemosiderosis, chronic hemolytic anemia with frequent blood transfusions).

Extreme caution during injection of a contrast agent is necessary to avoid extravasation. This is especially important in patients with severe arterial or venous disease.

Repeat Procedures: If the physician determines that imaging needs to be repeated, based on the pharmacodynamics of Feridex I.V., repeat images could be obtained up to 3.5 hours after the original infusion without re-injection. Data on timing for and safety of repeated injections are not available. (**See CLINICAL PHARMACOLOGY section.**)

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Information for Patients

Patients receiving Feridex I.V. should be instructed to inform their physician or health care provider:

1. If you are pregnant or nursing. **(See PRECAUTIONS—PREGNANCY—Teratogenic Effects—Pregnancy Category C section.)**
2. If you are allergic to iron or dextran containing drugs or if you had any reactions to previous injections of dyes used for x-ray procedures. Also, inform your physician or health care provider if you are allergic to any other drugs or food, or if you have immune, autoimmune or immune deficiency disorders. **(See PRECAUTIONS—GENERAL section.)**
3. About all medications you are currently taking, including non-prescription (over-the-counter) drugs and vitamins, before you have this procedure.

Patients should be informed that:

1. Feridex I.V. has been prescribed for liver enhancement during MRI.
2. Feridex I.V. may cause severe back, groin, leg, or other pain, or allergic reactions.
3. The infusion fluid is a dark color.
4. The skin surrounding the infusion site may discolor if there is extravasation. The discoloration should disappear over time.

Drug Interactions

Drug interactions were not noted and were not studied in clinical studies. (**See CLINICAL PHARMACOLOGY section on Drug-Drug Interactions.**)

Feridex I.V. administration provides elemental iron. In patients who are receiving supplemental iron orally or parenterally, the dose of supplemental iron may need to be decreased.

The effect of concomitant parenteral iron on Feridex I.V. dosing is not known. (**See CLINICAL PHARMACOLOGY section.**)

LABORATORY TEST FINDINGS

Serum iron levels may be above the normal range following Feridex I.V. administration. Transient increases in serum iron of 15–100% of baseline were observed 18 to 24 hours after Feridex I.V. administration, and returned to normal in most patients by 7 days after administration. Increases in serum ferritin levels were seen 1 to 7 days after administration.

(See CLINICAL PHARMACOLOGY, PHARMACOKINETICS section.)

In a Phase 1 study in normal subjects, PTT was statistically significantly increased; however, all values were within the normal range and no subjects had a more than 40% increase from baseline. In clinical trials of patients who had baseline hematologic abnormalities associated with underlying liver disease, an effect of Feridex I.V. on platelet or PTT was not demonstrated.

In patients with low hematocrit and hemoglobin, over a period of 48 hours to 7 days after Feridex I.V., the serum iron, the hematocrit and hemoglobin levels increase slightly.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long term studies in animals have not been performed to evaluate the carcinogenic potential of Feridex I.V. Therapeutic iron dextran products have been associated with the development of sarcomas at the intramuscular injection sites; the length of treatment or the length of time after injection until development of tumor is not known. Ferumoxides are iron oxides associated with dextran. Whether Feridex I.V. has a risk of tumorigenesis that is similar to that of iron dextran is not known.

Feridex I.V. was not genotoxic in a series of studies that included the Ames test, the CHO/HGPRT forward mutation assay, a chromosome aberration test in CHO cells, an unscheduled DNA synthesis assay, and a micronucleus assay in mice.

Feridex I.V. did not impair the fertility of male or female rats at dosages that were up to approximately 5 times the clinical dose when normalized to body surface area.

PREGNANCY

Teratogenic Effects.

Pregnancy Category C. Feridex I.V. is teratogenic in rabbits at all studied doses. The smallest dose studied was approximately six times the clinical dose when normalized to body surface area. Adequate and well controlled studies were not conducted in pregnant women. Feridex I.V. should be used during pregnancy only if the potential benefit justifies the potential risk.

NURSING MOTHERS

It is not known whether Feridex I.V. is excreted in human milk. This drug should only be used in nursing women if the benefit clearly outweighs the risk.

PEDIATRIC USE

Safety and efficacy of Feridex I.V. in the pediatric population have not been established.

ADVERSE REACTIONS

In clinical trials, a total of 2240 subjects (32 healthy volunteers and 2208 patients with known or suspected liver lesions) received Feridex I.V. Of these subjects, 35% received the recommended dose of 0.56 mg Fe/kg and 62% received a dose of 0.84 mg Fe/kg. Forty-four percent were female and 56% were male, with a mean age of 54.9 years (range 11–89).

Of 866 subjects in whom race is known, 647 (75%) were Asian, 199 (22%) were Caucasian, 14 (2%) were Black, 3 (<1%) were Hispanic, and 3 (<1%) other. Racial demographic information was not available for the 1374 subjects in European clinical trials.

Of the 2240 subjects, 197 (8.8%) experienced an adverse event. The most commonly noted adverse experiences were back pain (3.4%), and vasodilation (2.3%).

In a subgroup of 1535 patients in controlled clinical trials, in 44 (2.9%) of the patients [9/226 (3.9%) in US, 10/635 (1.6%) in Japanese, and 25/674 (3.7%) in European studies] the infusion was interrupted or discontinued because of acute, moderate to severe pain (back, lower torso, chest, groin, or upper leg) with or without hypotension. Some patients required treatment. In a few of the patients with pain 11/44 (25%), the infusion was interrupted, restarted, and completed. (**See WARNINGS section.**)

Pain in any location was reported in 4.2% of these 1535 patients given Feridex I.V.

In a subgroup of 689 patients in whom associated underlying disorders were evaluated, back pain occurred in 18/144 (12.5%) patients with cirrhosis and in 10/545 (1.8%) patients who did not have cirrhosis. The frequency of pain in patients with other liver abnormalities is not known.

Anaphylactic and allergic adverse events (e.g., generalized urticaria, respiratory symptoms, and hypotension) that required acute treatment occurred in 11/2240 (0.5%) of patients who received Feridex I.V.

Most other adverse reactions were mild to moderate, of short duration, and resolved spontaneously without treatment. A relationship between adverse events and dose, age, or gender was not observed.

Adverse reactions that occurred in greater than or equal to 0.5% of the 1535 patients in controlled clinical trials are listed below in related categories, in decreasing order of occurrence within each system, and regardless of causality:

ADVERSE EVENTS IN≥0.5% OF THE 1535 PATIENTS IN CONTROLLED CLINICAL TRIALS WITH FERIDEX I.V.

Categories	Adverse Event	Number of Patients (%)
Number of patients who received Feridex I.V.		1535
Number of patients with any adverse event		144 (9.4%)
Digestive System	Nausea	11 (0.7%)
Body as a whole	Total (pain all sources) Pain Back/Leg/Pain Leg Headache Pain Chest	65 (4.2%) 56 (3.6%) 13 (0.8%) 10 (0.7%)
Hypersensitivity	Total (hypersensitivity all sources) Vasodilation Urticaria/Erythematous Rash/Rash Dyspnea	53 (3.4%) 33 (2.1%) 12 (0.7%) 8 (0.5%)

The following adverse reactions were observed in <0.5% of the subjects receiving Feridex I.V.: DIGESTIVE: diarrhea, vomiting, anorexia; BODY PAIN: pain abdomen, pain neck, fatigue, fever; CARDIOVASCULAR: hypertension, hypotension, arrhythmias; NERVOUS: dizziness, paresthesia; SKIN AND APPENDAGES: pruritus, sweating; SPECIAL SENSES: abnormal vision, taste perversion; RESPIRATORY: cough, epistaxis, rhinitis.

(See sections on CONTRAINDICATIONS, WARNINGS and PRECAUTIONS.)

In 705 patients who received Feridex I.V. in other trials, similar adverse events were reported.

OVERDOSE

Overdose with Feridex I.V. has not been reported. Acute toxicity is apt to be related to iron overload, acute back pain and allergic events. Chronic administration of therapeutic iron dextran in excess of the total amount of iron needed for iron stores may lead to hemosiderosis.

A study of (59Fe) complexed iron-dextran utilizing isotonic saline in a 4-hour in vitro dialysis run indicated that less than 0.5% of the injected radio labeled iron dextran traversed the dialysis membrane. Feridex I.V. contains iron associated with dextran. Whether Feridex I.V. is dialyzable is not known.

DOSAGE AND ADMINISTRATION

Dose

The recommended dosage of Feridex I.V. is 0.56 milligrams of iron (0.05 mL Feridex I.V.) per kilogram of body weight, that is diluted in 100 mL of 5% dextrose solution and given over 30 minutes. (See Drug Preparation Section). The diluted drug is administered through a 5 micron filter at a rate of 2 to 4 milliliters per minute.

Feridex I.V. should not be administered undiluted.

Drug Preparation

1. The vial should be used at room temperature. Mix by inverting the vial 10 to 20 times.
2. Draw up the appropriate dose of Feridex I.V. into a sterile syringe.
3. Dilute Feridex I.V. by injecting it into 100 mL of 5% dextrose solution (D5W).
4. The bag should be inverted two or three times to assure dilution.
5. The drug product should be administered within 8 hours following dilution.

Imaging

Post-contrast imaging may begin immediately after the dose is infused and may be performed up to 3.5 hours after the end of the infusion. T2-weighted pulse sequences provide the maximum contrast effect.

HOW SUPPLIED

Feridex I.V. is black to reddish brown liquid containing 11.2 mg Fe/mL (56 mg of iron/vial) in a vial with a tear off seal. Feridex I.V. is supplied in 5 mL single dose vials in boxes of 1 (NDC 59338-7035-1) and 5 (NDC 59338-7035-5). An administration filter is supplied for each vial.

Feridex I.V. is stable for 24 hours after dilution.

STORAGE

Storage at 2–30 °C (35–86 °F). DO NOT FREEZE.

If there are indications that the package has been exposed to freezing, DO NOT USE.

Rx Only

The following patents have claims directed to the drug: U.S.P. 4,770,183, U.S.P. 4,827,945, U.S.P. 4,951,675, U.S.P. 5,055,288, U.S.P. 5,102,652, U.S.P. 5,219,554, U.S.P. 5,248,492

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