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DEXFERRUM®
(IRON DEXTRAN INJECTION, USP)
Rx Only

WARNING: RISK FOR ANAPHYLACTIC-TYPE REACTIONS

Anaphylactic-type reactions, including fatalities, have followed the parenteral administration of iron dextran injection.

- **Have resuscitation equipment and personnel trained in the detection and treatment of anaphylactic-type reactions readily available during Dexferrum administration.**
- **Administer a test Dexferrum dose prior to the first therapeutic dose. If no signs or symptoms of anaphylactic-type reactions follow the test dose, administer the full therapeutic Dexferrum dose.**
- **During all Dexferrum administrations, observe for signs or symptoms of anaphylactic-type reactions. Fatal reactions have followed the test dose of iron dextran injection. Fatal reactions have also occurred in situations where the test dose was tolerated.**
- **Use Dexferrum only in patients in whom clinical and laboratory investigations have established an iron deficient state not amenable to oral iron therapy.**
- **Patients with a history of drug allergy or multiple drug allergies may be at increased risk of anaphylactic-type reactions to Dexferrum.**

DESCRIPTION: DEXFERRUM® (IRON DEXTRAN INJECTION, USP) is a dark brown, slightly viscous sterile liquid complex of ferric oxyhydroxide for intravenous use. Each mL contains: 50 mg elemental iron as an iron dextran complex. Sodium chloride may have been added for tonicity. Water for injection q.s. pH (range 4.5-7.0) adjusted with hydrochloric acid and, if necessary, sodium hydroxide. Sterile, nonpyrogenic.

Therapeutic Class: Hematinic

CLINICAL PHARMACOLOGY: General: Circulating iron dextran is removed from the plasma by cells of the reticuloendothelial system, which split the complex into its components of iron and dextran. The iron is immediately bound to the available protein moieties to form hemosiderin or ferritin, the physiological forms of iron, or to a lesser extent to transferrin. This iron which is subject to physiological control replenishes hemoglobin and depleted iron stores.

Dextran, a polyglucose, is either metabolized or excreted. Negligible amounts of iron are lost via the urinary or alimentary pathways after administration of iron dextran.

Studies involving intravenously administered iron dextran to iron deficient subjects who had coexisting end-stage renal disease and other clinical problems, have yielded individual half-life values ranging from 9.4 to 87.4 hours. The average half-life value equaled 58.9 hours. These studies measured the total serum iron directly as well as the transferrin-bound iron, non-radio-isotopically. It should be understood that these half-life values do not represent clearance of iron from the body. Iron is not

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easily eliminated from the body and accumulation of iron can be toxic.

In vitro studies have shown that removal of iron dextran by dialysis is negligible[1,2]. Six different dialyzer membranes were investigated (polysulphone, cuprophane, cellulose acetate, cellulose triacetate, polymethylmethacrilate and polyacrylonitrile), including those considered high efficiency and high flux.

INDICATIONS AND USAGE: Dexferrum is indicated for treatment of patients with documented iron deficiency in whom oral administration is unsatisfactory or impossible.

CONTRAINDICATIONS: Hypersensitivity to the product. All anemias not associated with iron deficiency.

WARNINGS:

Risk for Anaphylactic-type Reactions: Anaphylactic-type reactions, including fatalities, have followed the parenteral administration of iron dextran. Always have resuscitation equipment and personnel trained in the detection and treatment of anaphylactic-type reactions readily available during Dexferrum adminisration. Prior to the first therapeutic dose, administer a test Dexferrum dose of 0.5 mL intravenously at a gradual rate over at least five minutes. Although reactions are usually evident within a few minutes, observe patients for at least one hour before administering the therapeutic dose. During all Dexferrum administrations, observe patients for signs or symptoms of anaphylactic-type reactions. Fatal reactions have followed the test dose of iron dextran and have also occurred in situations where the test dose was tolerated. Use Dexferrum only in patients in whom clinical and laboratory investigations have established an iron deficient state not amenable to oral iron therapy.

The factors that affect the risk for anaphylactic-type reactions to iron dextran products are not fully known but limited clinical data suggest the risk may be increased among patients with a history of drug allergy or multiple drug allergies. Additionally, concomitant use of angiotensin-converting enzyme inhibitor drugs may increase the risk for reactions to an iron dextran product. The extent of risk for anaphylactic-type reactions following exposure to any specific iron dextran product is unknown and may vary among the products. Iron dextran products differ in chemical characteristics and may differ in clinical effects. Iron dextran products are not clinically interchangeable.

Delayed Reactions: Large intravenous doses, such as used with total dose infusions (TDI), have been associated with an increased incidence of adverse effects. The adverse effects frequently are delayed (1-2 days) reactions typified by one or more of the following symptoms: arthralgia, backache, chills, dizziness, moderate to high fever, headache, malaise, myalgia, nausea, and vomiting. The onset is usually 24-48 hours after administration and symptoms generally subside within 3-4 days. The etiology of these reactions is not known. The potential for a delayed reaction must be considered when estimating the risk/benefit of treatment.

The maximum daily dose should not exceed 2 mL undiluted iron dextran.

Risks in Patients with Underlying Conditions: Dexferrum should be used with extreme care in patients with serious impairment of liver function. It should not be used during the acute phase of infectious kidney disease.

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Adverse reactions experienced following administration of Dexferrum may exacerbate cardiovascular complications in patients with pre-existing cardiovascular disease.

Carcinogenesis: A risk of carcinogenesis may attend the intramuscular injection of iron-carbohydrate complexes. Such complexes have been found under experimental conditions to produce sarcoma when large doses or small doses injected repeatedly at the same site were given to rats, mice, and rabbits, and possibly in hamsters.

The long latent period between the injection of a potential carcinogen and the appearance of a tumor makes it impossible to measure accurately the risk in man. There have, however, been several reports in the literature describing tumors at the injection site in humans who had previously received intramuscular injections of iron-carbohydrate complexes.

PRECAUTIONS: General: Unwarranted therapy with parenteral iron will cause excess storage of iron with the consequent possibility of exogenous hemosiderosis. Such iron overload is particularly apt to occur in patients with hemoglobinopathies and other refractory anemias that might be erroneously diagnosed as iron deficiency anemias.

Dexferrum should be used with caution in individuals with histories of significant allergies and/or asthma.

Anaphylaxis and other hypersensitivity reactions have been reported after uneventful test doses as well as therapeutic doses of iron dextran injection. Therefore, administer a test dose prior to the first administration of Dexferrum. (See **BOXED WARNING** and **DOSAGE AND ADMINISTRATION**).

Epinephrine should be immediately available in the event of acute hypersensitivity reactions. (Usual adult dose: 0.5 mL of a 1:1000 solution, by subcutaneous or intramuscular injection.) **Note:** Patients using beta-blocking agents may not respond adequately to epinephrine. Isoproterenol or similar beta-agonist agents may be required in these patients.

Patients with rheumatoid arthritis may have an acute exacerbation of joint pain and swelling following the administration of Dexferrum.

Information For Patients: Patients should be advised of the potential adverse reactions associated with the use of Dexferrum.

Drug/Laboratory Test Interactions: Large doses of iron dextran (5 mL or more) have been reported to give a brown color to serum from a blood sample drawn 4 hours after administration.

The drug may cause falsely elevated values of serum bilirubin and falsely decreased values of serum calcium.

Serum iron determinations (especially by colorimetric assays) may not be meaningful for 3 weeks following the administration of iron dextran.

Serum ferritin peaks approximately 7 to 9 days after an intravenous dose of Dexferrum and slowly returns to baseline after about 3 weeks.

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Examination of the bone marrow for iron stores may not be meaningful for prolonged periods following iron dextran therapy because residual iron dextran may remain in the reticuloendothelial cells.

Bone scans with 99m Tc-labeled bone seeking agents, in the presence of high serum ferritin levels or following iron dextran infusions, have been reported to show reduction of bony uptake, marked renal activity, and excessive blood pool and soft tissue accumulation.

Carcinogenesis, Mutagenesis, Impairment of Fertility: See **WARNINGS.**

Pregnancy: *Teratogenic Effects, Pregnancy Category C*: Iron dextran has been shown to be teratogenic and embryocidal in mice, rats, rabbits, dogs, and monkeys when given in doses of about 3 times the maximum human dose.

No consistent adverse fetal effects were observed in mice, rats, rabbits, dogs and monkeys at doses of 50 mg iron/kg or less. Fetal and maternal toxicity has been reported in monkeys at a total intravenous dose of 90 mg iron/kg over a 14 day period. Similar effects were observed in mice and rats on administration of a single dose of 125 mg iron/kg. Fetal abnormalities in rats and dogs were observed at doses of 250 mg iron/kg and higher. The animals used in these tests were not iron deficient. There are no adequate and well-controlled studies in pregnant women. Dexferrum should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Placental Transfer: Various animal studies and studies in pregnant humans have demonstrated inconclusive results with respect to the placental transfer of iron dextran as iron dextran. It appears that some iron does reach the fetus, but the form in which it crosses the placenta is not clear.

Nursing Mothers: Caution should be exercised when Dexferrum is administered to a nursing woman. Traces of unmetabolized iron dextran are excreted in human milk.

Pediatric Use: Not recommended for use in infants under 4 months of age (See **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS: Severe/Fatal: Anaphylactic reactions have been reported with the use of iron dextran injection; on occasions these reactions have been fatal. Such reactions, which occur most often within the first several minutes of administration, have been generally characterized by sudden onset of respiratory difficulty and/or cardiovascular collapse. Because fatal anaphylactic reactions have been reported after administration of iron dextran injection, the drug should be given only when resuscitation techniques and treatment of anaphylactic and anaphylactoid shock are readily available. (See **BOXED WARNING** and **PRECAUTIONS: General**, pertaining to immediate availability of epinephrine.)

Cardiovascular: Chest pain, chest tightness, shock, cardiac arrest, hypotension, hypertension, tachycardia, bradycardia, flushing, arrhythmias. (Flushing and hypotension may occur from too rapid injections by the intravenous route.)

Dermatologic: Urticaria, pruritus, purpura, rash, cyanosis.

Gastrointestinal: Abdominal pain, nausea, vomiting, diarrhea.

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Hematologic/lymphatic: Leucocytosis, lymphadenopathy.

Musculoskeletal/soft tissue: Arthralgia, arthritis (may represent reactivation in patients with quiescent rheumatoid arthritis -See **PRECAUTIONS: General**), myalgia; backache; sterile abscess; brown skin and/or underlying tissue discoloration (staining); cellulitis; swelling; inflammation; local phlebitis at or near intravenous injection site.

Neurologic: Convulsions, seizures, syncope, headache, weakness, unresponsiveness, paresthesia, febrile episodes, chills, dizziness, disorientation, numbness, unconsciousness.

Respiratory: Respiratory arrest, dyspnea, bronchospasm, wheezing.

Urologic: Hematuria.

Delayed reactions: Arthralgia, backache, chills, dizziness, fever, headache, malaise, myalgia, nausea, vomiting (See **WARNINGS**).

Miscellaneous: Febrile episodes, sweating, shivering, chills, malaise, altered taste.

OVERDOSAGE: Overdosage with iron dextran is unlikely to be associated with any acute manifestations. Dosages of iron dextran in excess of the requirements for restoration of hemoglobin and replenishment of iron stores may lead to hemosiderosis. Periodic monitoring of serum ferritin levels may be helpful in recognizing a deleterious progressive accumulation of iron resulting from impaired uptake of iron from the reticuloendothelial system in concurrent medical conditions such as chronic renal failure, Hodgkins disease, and rheumatoid arthritis. The LD_{50} of iron dextran is not less than 500 mg/kg in the mouse.

DOSAGE AND ADMINISTRATION: Oral iron should be discontinued prior to administration of Dexferrum.

Dosage:

I. *Iron Deficiency Anemia*: Periodic hematologic determination (hemoglobin and hematocrit) is a simple and accurate technique for monitoring hematological response, and should be used as a guide in therapy. It should be recognized that iron storage may lag behind the appearance of normal blood morphology. Serum iron, total iron binding capacity (TIBC) and percent saturation of transferrin are other important tests for detecting and monitoring the iron deficient state.

After administration of iron dextran complex, evidence of a therapeutic response can be seen in a few days as an increase in the reticulocyte count.

Although serum ferritin is usually a good guide to body iron stores, the correlation of body iron stores and serum ferritin may not be valid in patients on chronic renal dialysis who are also receiving iron dextran complex.

Although there are significant variations in body build and weight distribution among males and females, the accompanying table and formula represent a convenient means for estimating the total iron required. This total iron requirement reflects the amount of iron needed to restore hemoglobin concentration to normal or near normal levels plus an additional allowance to provide adequate

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replenishment of iron stores in most individuals with moderately or severely reduced levels of hemoglobin. It should be remembered that iron deficiency anemia will not appear until essentially all iron stores have been depleted. Therapy, thus, should aim at not only replenishment of hemoglobin iron but iron stores as well.

Factors contributing to the formula are shown below.

$$\frac{\text{mg blood iron}}{\text{lb body weight}} = \frac{\text{mL blood}}{\text{lb body weight}} \times \frac{\text{g hemoglobin}}{\text{mL blood}} \times \frac{\text{mg iron}}{\text{g hemoglobin}}$$

a) Blood volume……..65 mL/kg of body weight
b) Normal hemoglobin (males and females)
over 15 kg (33 lbs)……..14.8 g/dl
15 kg (33 lbs) or less……...12 g/dl
c) Iron content of hemoglobin…….0.34%
d) Hemoglobin deficit
e) Weight

Based on the above factors, individuals with normal hemoglobin levels will have approximately 33 mg of blood iron per kilogram of body weight (15 mg/lb).

Note: The table and accompanying formula are applicable for dosage determinations only in patients with iron deficiency anemia; they are not to be used for dosage determinations in patients requiring iron replacement for blood loss.

TOTAL DEXFERRUM® REQUIREMENT FOR HEMOGLOBIN RESTORATION AND IRON STORES REPLACEMENT*

PATIENT LEAN BODY WEIGHT		Milliliter Requirement of Dexferrum Based On Observed Hemoglobin of							
kg	lb	**3** (g/dl)	**4** (g/dl)	**5** (g/dl)	**6** (g/dl)	**7** (g/dl)	**8** (g/dl)	**9** (g/dl)	**10** (g/dl)
5	11	3	3	3	3	2	2	2	2
10	22	7	6	6	5	5	4	4	3
15	33	10	9	9	8	7	7	6	5
20	44	16	15	14	13	12	11	10	9
25	55	20	18	17	16	15	14	13	12
30	66	23	22	21	19	18	17	15	14
35	77	27	26	24	23	21	20	18	17
40	88	31	29	28	26	24	22	21	19
45	99	35	33	31	29	27	25	23	21
50	110	39	37	35	32	30	28	26	24
55	121	43	41	38	36	33	31	28	26
60	132	47	44	42	39	36	34	31	28
65	143	51	48	45	42	39	36	34	31
70	154	55	52	49	45	42	39	36	33
75	165	59	55	52	49	45	42	39	35
80	176	63	59	55	52	48	45	41	38
85	187	66	63	59	55	51	48	44	40
90	198	70	66	62	58	54	50	46	42
95	209	74	70	66	62	57	53	49	45
100	220	78	74	69	65	60	56	52	47

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105	231	82	77	73	68	63	59	54	50
110	242	86	81	76	71	67	62	57	52
115	253	90	85	80	75	70	64	59	54
120	264	94	88	83	78	73	67	62	57

*Table values were calculated based on a normal adult hemoglobin of 14.8 g/dl for weights greater than 15 kg (33 lbs) and a hemoglobin of 12.0 g/dl for weights less than or equal to 15 kg (33 lbs).

The total amount of Dexferrum in mL required to treat the anemia and replenish iron stores may be approximated as follows:

Adults and Children over 15 kg (33 lbs): See Dosage Table. Alternatively the total dose may be calculated:

Dose (mL) = 0.0442 (Desired Hb - Observed Hb) x LBW + (0.26 x LBW)

Based on: Desired Hb = the target Hb in g/dl.

Observed Hb = the patient's current hemoglobin in g/dl.

LBW = Lean body weight in kg. A patient's lean body weight (or actual body weight if less than lean body weight) should be utilized when determining dosage.

For males: LBW = 50 kg + 2.3 kg for each inch of patient's height over 5 feet

For females: LBW = 45.5 kg + 2.3 kg for each inch of patient's height over 5 feet

To calculate a patient's weight in kg when lbs are known:

$$\frac{\text{patient's weight in pounds}}{2.2} = \text{weight in kilograms}$$

Children 5 -15 kg (11 -33 lbs)*:* See Dosage Table.

Dexferrum should not normally be given in the first four months of life. (See **PRECAUTIONS: Pediatric Use**)

Alternatively the total dose may be calculated:

Dose (mL) = 0.0442 (Desired Hb - Observed Hb) x W + (0.26 x W)

Based on: Desired Hb = the target Hb in g/dl. (Normal Hb for Children 15 kg or less is 12 g/dl)

W = Weight in kg.

To calculate a patient's weight in kg when lbs are known:

$$\frac{\text{patient's weight in pounds}}{2.2} = \text{weight in kilograms}$$

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II. *Iron Replacement for Blood Loss:* Some individuals sustain blood losses on an intermittent or repetitive basis. Such blood losses may occur periodically in patients with hemorrhagic diatheses (familial telangiectasia; hemophilia; gastrointestinal bleeding) and on a repetitive basis from procedures such as renal hemodialysis.

Iron therapy in these patients should be directed toward replacement of the equivalent amount of iron represented in the blood loss. The table and formula described under **I. *Iron Deficiency Anemia*** are ***not*** applicable for simple iron replacement values.

Quantitative estimates of the individual's periodic blood loss and hematocrit during the bleeding episode provide a convenient method for the calculation of the required iron dose.

The formula shown below is based on the approximation that 1 mL of normocytic, normochromic red cells contains 1 mg of elemental iron:

Replacement iron (in mg) = Blood loss (in mL) x hematocrit
Example: Blood loss of 500 mL with 20% hematocrit
Replacement Iron = 500 x 0.20 = 100 mg

$$\text{Dexferrum dose} = \frac{100\text{ mg}}{50} = 2\text{ mL}$$

Administration: The total amount of Dexferrum required for the treatment of iron deficiency anemia or iron replacement for blood loss is determined from the table or appropriate formula (See **Dosage**).

Dexferrum is administered by intravenous injection. PRIOR TO THE FIRST DEXFERRUM THERAPEUTIC DOSE, ADMINISTER A TEST DOSE OF 0.5 ML INTRAVENOUSLY (See **BOXED WARNING** and **PRECAUTIONS**). ADMINISTER THE TEST DOSE AT A GRADUAL RATE OVER AT LEAST FIVE MINUTES. Although anaphylactic reactions known to occur following Dexferrum administration are usually evident within a few minutes, or sooner, it is recommended that a period of an hour or longer elapse before the remainder of the initial therapeutic dose is given.

Individual doses of 2 mL or less may be given on a daily basis until the calculated total amount required has been reached. Dexferrum is given undiluted at a **slow gradual rate** not to exceed 50 mg (1 mL) per minute.

If no adverse reactions are observed, Dexferrum can be given according to the following schedule until the calculated total amount required has been reached. Each day's dose should ordinarily not exceed 0.5 mL (25 mg of iron) for infants under 5 kg (11 lbs); 1 mL (50 mg of iron) for children under 10 kg (22 lbs); and 2 mL (100 mg of iron) for other patients.

NOTE: Do not mix Dexferrum with other medications or add to parenteral nutrition solutions for intravenous infusion.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever the solution and container permit.

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HOW SUPPLIED: Dexferrum® (Iron Dextran Injection, USP) containing 50 mg of elemental iron per mL.

NDC 0517-0234-10	2 mL Single Dose Vial	Packaged in boxes of 10
NDC 0517-0134-10	1 mL Single Dose Vial	Packaged in boxes of 10

Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) (See USP Controlled Room Temperature).

REFERENCES:

1. Hatton RC, Portales IT, Finley A, Ross EA. Removal of Iron Dextran by Hemodialysis: An *In Vitro* Study. *Am. J Kid Dis.* 1995; 26(2):327-330.

2. Manuel MA, Stewart WK, St. Clair Neill GD, Hutchinson F. Loss of Iron-Dextran through Cuprophane Membrane of a Disposable Coil Dialyser. *Nephron*. 1972; 9:94-98.

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