99-1-19

Imferon®

(iron dextran injection, USP)

CAUTION: Federal law prohibits dispensing without prescription.

WARNING:

THE PARENTERAL USE OF COMPLEXES OF IRON AND CARBOHYDRATES HAS RESULTED IN ANAPHYLACTIC-TYPE REACTIONS. DEATHS ASSOCIATED WITH SUCH ADMINISTRATION HAVE BEEN REPORTED. THEREFORE, IMFERON SHOULD BE USED ONLY IN THOSE PATIENTS IN WHOM THE INDICATIONS HAVE BEEN CLEARLY ESTABLISHED AND LABORATORY INVESTIGATIONS CONFIRM AN IRON DEFICIENT STATE NOT AMENABLE TO ORAL IRON THERAPY.

DESCRIPTION: IMFERON (iron dextran injection, USP) is a dark brown, slightly viscous sterile liquid complex of ferric oxyhydroxide and low molecular weight dextran derivative in approximately 0.9% w/v sodium chloride for intravenous or intramuscular use. It contains the equivalent of 50 mg elemental iron (as an iron dextran complex) per mL. The pH of the solution is between 5.2 and 6.5. The multiple dose vial also contains 0.5% w/v phenol (for intramuscular use only).

Electron microscopy has shown the molecule to have an inner electron-dense FeOOH core with a diameter approximating 3 nm and an outer plastic (moldable) dextran shell with a diameter of approximately 13 nm. Almost all the iron (98-99%) is present as a stable ferric-dextran complex. The remaining iron represents a very weak ferrous complex.

Therapeutic Class: Hematinic

CLINICAL PHARMACOLOGY: *General:* After intramuscular injection, iron dextran is absorbed from the injection site into the capillaries and the lymphatic system. 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. When iron dextran is administered during hemodialysis only negligible amounts may cross the dialysis membranes.

The major portion of intramuscular injections of iron dextran is absorbed within 72 hours; most of the remaining iron is absorbed over the ensuing 3 to 4 weeks. Staining from inadvertent deposition of iron dextran in subcutaneous and/or cutaneous tissues usually resolves or fades within several weeks or months; in some rare instances, however, such stains have been reported to persist for several years.

Various studies involving intravenously administered [59Fe] iron dextran to iron deficient subjects, some of whom had coexisting diseases, have yielded half-life values ranging from 5 hours to more than 20 hours. The 5-hour value was determined for [59Fe] iron dextran from a study that used laboratory methods to separate the circulating [59Fe] iron dextran from the transferrin-bound [59Fe]. The 20-hour value reflects a half-life determined by measuring total [59Fe], both circulating and bound. It should be understood that these half-life values do not represent clearance of iron from the body. Iron is not easily eliminated from the body and accumulation of iron can be toxic.

INDICATIONS: Intravenous or intramuscular injections of iron dextran are 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: See Boxed WARNING.
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.

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 (such symptoms have been well recognized since iron dextran was first used). These symptoms have also been reported following intramuscular injection and usually subside within 3-7 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 intravenous daily dose should not exceed 2 mL undiluted iron dextran.

This preparation 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.

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

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.

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

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.

Reports in the literature from countries outside the United States (in particular, New Zealand) have suggested that the use of intramuscular iron dextran in neonates has been associated with an increased incidence of gram-negative sepsis, primarily due to *E. coli*. This effect from the use of IMFERON in the United States has not been reported.

Information for Patients: Patients should be advised of the potential adverse reactions associated with the use of IMFERON.

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 billrubin and falsely decreased values of serum calcium.

Serum iron determinations by colorimetric assays may not be meaningful for 3 weeks following the administration of iron dextran, particularly after large intravenous doses.

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

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.

Prolongation of the partial thromboplastin time has been reported to occur after intravenous administration of iron dextran when the blood sample for the test is mixed with anticoagulant citrate dextrose solution, USP. This interference apparently does not occur when anticoagulant sodium citrate solution, USP is used. Blood-typing and cross-matching are not affected by iron dextran.

Bone scans involving 99mTc-diphosphonate have been reported to show a dense, crescentic area of activity in the buttocks, following the contour of the iliac crest, 1 to 6 days after intramuscular injections of IMFERON.

Bone scans with 99mTc-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.

Caution should be used in interpreting results of serum iron measurements when blood samples are obtained within 1 or 2 weeks of administration of large doses of IMFERON.

Carcinogenesis, Mutagenesis, Impairment of Fertility: See WARNINGS.

Pregnancy: Pregnancy Category C. IMFERON 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. IMFERON 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 IMFERON is administered to a nursing woman. Only traces of unmetabolized iron dextran are excreted in human milk.

Pediatric Usage: 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 IMFERON; on rare 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. The incidence of these acute hypersensitivity reactions has been estimated between 0.2% to 0.3%. (See boxed WARNING and PRECAUTIONS, *General*, pertaining to immediate availability of epinephrine.)

Mild/moderate: Delayed reactions (see WARNINGS). The incidence of delayed reactions reported in a longitudinal study of patients given multiple intravenous injections of IMFERON, usually 5 mL or greater, was approximately 8% (4% of the total number of injections given).

Other systemic/local: Isolated or multiple signs/symptoms with varying severity have been reported.

Cardiovascular: Chest pain, shock, hypotension, tachycardia, flushing.
(Flushing and hypotension may occur from too rapid injections by the I.V. route.)
Dermatologic: Urticaria, pruritus, purpura, rash.
Gastrointestinal: Abdominal pain, nausea, vomiting, diarrhea.
Hematologic/lymphatic: Leucocytosis, lymphadenopathy (generally inguinal and associated with I.M. injections).

Musculoskeletal/soft tissue: Arthralgia, arthritis (may represent reactivation in patients with quiescent rheumatoid arthritis — see PRECAUTIONS, *General*), myalgia, including backache; abscess formation (sterile); necrosis; atrophy/fibrosis (I.M. injection site); cellulitis, swelling; brown skin and/or underlying tissue discoloration (staining) (See CLINICAL PHARMACOLOGY), soreness or pain at or near intramuscular injection sites, which in some isolated instances was reported to persist for over a year; variable degree of inflammation; local phlebitis at or near I.V. injection site.

Neurologic: Convulsions (may accompany anaphylaxis), syncope, headache, weakness, paresthesia, febrile episodes, chills.
Respiratory: Bronchospasm, dyspnea.
Urologic: Hematuria.
Miscellaneous: Febrile episodes, sweating, chills.

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* The human dose presented here is the total iron required for treating an iron deficient state in a representative patient. The calculation represents a 50 kg patient with a hemoglobin value of 8 g/dl requiring 30 mL of IMFERON or 1500 mg iron — equivalent to 30 mg/kg.

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OVERDOSAGE: Overdosage with IMFERON is unlikely to be associated with any acute manifestations. Excessive doses of IMFERON beyond 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 IMFERON is not less than 500 mg/kg in the mouse.

Dialysis: A study of [59Fe] iron dextran utilizing isotonic saline in a 4-hour in vitro dialysis run, indicated that less than 0.5% of the injected radiolabeled iron dextran traversed the dialysis membrane.

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

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. If there has not been a 1 gram per 100 mL rise in hemoglobin within 2 weeks of starting iron dextran therapy, the diagnosis of iron deficiency anemia should be reviewed.

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 formulae 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 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 ..... 7.0% body weight

b) Normal hemoglobin (males and females)
over 15 kg (33 lbs.) ..... 14.8 g/100 mL
15 kg (33 lbs.) or less ..... 12.0 g/100 mL

c) Iron content of hemoglobin 0.34%

d) Weight

Based on the above factors, individuals with normal hemoglobin levels will have approximately 35 mg of blood iron per kilogram of body weight (16 mg/lb).

Note: The table and accompanying formulae 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 DOSE OF IMFERON IN ML
Observed Hemoglobin g/dl

Body Weight		3	4	5	6	7	8	9	10
kg	lb								
5	11	3	3	3	2	2	2	2	1
10	22	6	6	5	5	4	4	3	3
15	33	9	9	8	7	7	6	5	4
20	44	15	14	13	12	11	10	10	9
25	55	19	18	17	15	14	13	12	11
30	66	23	21	20	19	17	16	14	13
35	77	27	25	23	22	20	18	17	15
40	88	30	29	27	25	23	21	19	17
45	99	34	32	30	28	26	24	21	19
50	110	38	36	33	31	29	26	24	21
55	121	42	39	37	34	31	29	26	24
60	132	46	43	40	37	34	31	29	26
65	143	50	46	43	40	37	34	31	28
70	154	53	50	47	43	40	37	33	30
75	165	56	53	49	45	42	38	35	31
80	176	59	55	51	48	44	40	36	32
85	187	62	58	54	50	46	42	37	33
90	198	65	60	56	52	47	43	39	35
95	209	67	63	58	54	49	45	40	36
100	220	70	65	61	56	51	46	42	37
105	231	73	68	63	58	53	48	43	38
110	242	76	71	65	60	55	50	44	39
115	253	79	73	68	62	57	51	46	40
120	264	81	76	70	64	59	53	47	41

Dosage was calculated using the formula: Dose = 0.0476 x W x (Normal H − Observed H) + 1 mL per 5 kg to a maximum of 14 mL for iron stores.

Adults and Children over 15 kg (33 pounds):
See Dosage Table.
The total dose required may be calculated. If the patient's body weight in kilograms is W and the hemoglobin level is H g/dl:
Dose of IMFERON in mL required = 0.0476 x W x (14.8 − H) + iron stores.
Add 1 mL IMFERON for each 5 kg body weight to provide for the replenishment of iron stores to a maximum of 14 mL.
For weight in pounds use the factor 0.0216.

Children 5-15 kg (11-33 pounds):
See Dosage Table.
Alternatively the total dose may be calculated.
IMFERON should not normally be given in the first four months of life.
If the child's body weight in kilograms is W and hemoglobin level is H g/dl:
Dose of IMFERON required in mL = 0.0476 x W x (12 − H) + iron stores.
Add 1 mL IMFERON for each 5 kg body weight to provide for the replenishment of iron stores to a maximum of 14 mL.
For weight in pounds use the factor 0.0216.

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 lost blood. The table and formula presented under 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

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

Administration

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

I. *Intravenous Injection*

Prior to receiving their first intravenous IMFERON therapeutic dose, all patients should be given an intravenous *test dose* of 0.5 mL. Although anaphylactic reactions known to occur following IMFERON 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. IMFERON is given undiluted and *slowly* (1 mL or less per minute).

II. *Intramuscular Injection*

Prior to receiving their first intramuscular IMFERON therapeutic dose, all patients should be given an intramuscular *test dose* of 0.5 mL, administered in the same recommended test site and by the same technique as described below. Although anaphylactic reactions known to occur following IMFERON administration are usually evident within a few minutes or sooner, it is recommended that at least an hour or longer elapse before the remainder of the initial therapeutic dose is given.

If no adverse reactions are observed, IMFERON 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.); 1.0 mL (50 mg of iron) for children under 10 kg (22 lbs.); and 2.0 mL (100 mg of iron) for other patients.

Daily doses larger than these have been associated with an increased number of reports of delayed reactions and should be utilized only in those situations where the potential benefits clearly outweigh the increased risk. A daily dose of 5 mL should not be exceeded.

IMFERON should be injected only into the muscle mass of the upper outer quadrant of the buttock — never into the arm or other exposed areas — and should be injected deeply, with a 2-inch or 3-inch 19 or 20 gauge needle. If the patient is standing, he/she should be bearing his/her weight on the leg opposite the injection site, or if in bed, he/she should be in the lateral position with injection site uppermost. To avoid injection or leakage into the subcutaneous tissue, a Z-track technique (displacement of the skin laterally prior to injection) is recommended.

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

HOW SUPPLIED:

For intramuscular or intravenous use:
2 mL ampules, boxes of 10:
NDC 0585-2226-10

For intramuscular use ONLY:
10 mL multiple dose vial containing
0.5% phenol as a preservative, boxes of 2:
NDC 0585-3226-20

CAUTION: Federal law prohibits dispensing without prescription.

Store at room temperature, preferably below 86°F. Do not freeze. Keep out of the reach of children.

FISONS
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Made in England
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