

PRODUCT MONOGRAPH

 **DEXIRON[®]**

Iron Dextran Injection, USP
(50 mg Elemental Iron/ml)
1 ml, 2 ml Single-Dose Vials

THERAPEUTIC CLASSIFICATION

Haematinic - Iron Supplement

Manufactured by:

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Shirley, New York 11967

Date of Revision:
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Distributed by:

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2900 Argentia Road, Unit 10
Mississauga, Ontario
Canada L5N 7X9

Control number: 159452

NAME OF DRUG

DEXIRON®

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Serious Warnings and Precautions

- Serious hypersensitivity reactions including life threatening and fatal anaphylactic/anaphylactoid reactions have been reported in patients receiving intravenous iron products including DEXIRON (see WARNINGS and ADVERSE REACTIONS below).
- DEXIRON should only be administered when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions (see WARNINGS, PRECAUTIONS and ADVERSE REACTIONS below).

ACTIONS AND CLINICAL PHARMACOLOGY

DexIron® (Iron Dextran Injection, USP) is absorbed from intramuscular injection sites 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 haemosiderin or ferritin, the physiologic forms of iron, and to a lesser extent transferrin. This iron, which is subject to physiologic control, replenishes haemoglobin 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.

The major portion of iron dextran is absorbed within 72 hours after intramuscular injection. Most of the remaining iron dextran is absorbed over the ensuing 3 to 4 weeks.

Studies involving intravenously administered DexIron to iron deficient subjects who had coexisting end-stage renal disease and other clinical problems, yielded individual plasma half-lives ranging from 9.4 to 87.4 hours. The average half-life was 58.9 hours. These studies measured the total serum iron directly as well as the transferrin-bound iron, non-radioisotopically. 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.

The availability of iron for erythropoiesis and replenishment of iron stores after administration of DexIron was evaluated in a study of 20 renal dialysis patients. A total dose equivalent to 500 mg of iron, divided into five 100 mg doses was administered intravenously over a period of 10 days. (The dosing schedule varied according to each patient's clinical situation). Haemoglobin increased from a pre-treatment mean of 10.3 g/dl to 11.4 g/dl two weeks after completion of the series of injections. Serum ferritin and transferrin saturation peaked in one week at 620 ng/ml and 32%, respectively. Total iron binding capacity remained well within the physiological range (245-400 µg/dl) for the duration of the 30 day observation period, an indication that free ionic iron is not released from iron dextran. The mean percent utilization of iron from DexIron was calculated to be $47 \pm 20\%$.

INDICATIONS AND CLINICAL USE

DexIron is indicated for the treatment of patients with documented iron deficiency in whom oral iron administration is unsatisfactory or impossible. (See WARNINGS, DOSAGE & ADMINISTRATION).

CONTRAINDICATIONS

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

WARNINGS

THE PARENTERAL USE OF COMPLEXES OF IRON AND CARBOHYDRATES HAS RESULTED IN ANAPHYLACTIC-TYPE REACTIONS. DEATHS ASSOCIATED WITH SUCH ADMINISTRATION HAVE BEEN REPORTED. THEREFORE DEXIRON 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. SHOULD

HYPERSENSITIVITY REACTIONS OR SIGNS OF INTOLERANCE OCCUR, STOP DEXIRON IMMEDIATELY. MONITOR PATIENTS FOR SIGNS AND SYMPTOMS OF HYPERSENSITIVITY DURING AND AFTER DEXIRON ADMINISTRATION FOR AT LEAST 30 MINUTES TO 1 HOUR (SEE DOSAGE AND ADMINISTRATION). ONLY ADMINISTER DEXIRON WHEN PERSONNEL AND RESUSCITATIVE INTERVENTIONS ARE IMMEDIATELY AVAILABLE FOR THE TREATMENT OF SERIOUS HYPERSENSITIVITY REACTIONS.

A risk of carcinogenesis may attend the intramuscular injection of iron-carbohydrate complexes. Under experimental conditions iron dextran has been found to produce sarcomata when large doses were given to rodents, or when smaller doses were injected repeatedly into the same site in rodents and rabbits.

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

Large intravenous doses, such as those 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. These symptoms have also been reported following intramuscular injection and generally subside within 3-7 days. The etiology of these reactions is unknown. The potential for a delayed reaction must be considered when estimating the risks/benefits of treatment. The TDI method of administration is not currently recommended.

The maximum daily dose should not exceed 2 ml undiluted Iron Dextran Injection.

DexIron should be used with extreme care in patients with serious impairment of liver function.

DexIron should not be used during the acute phase of infectious kidney disease.

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

PRECAUTIONS

Unwarranted therapy with parenteral iron will cause excess storage of iron with the consequent possibility of iatrogenic haemosiderosis. Such iron overload is particularly apt to occur in patients with haemoglobinopathies and other refractory anemias that might be erroneously diagnosed as iron deficiency anemias.

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

Prior to receiving their first DexIron therapeutic dose, all patients should be given a test dose of 0.5 ml. (See DOSAGE & ADMINISTRATION). Since anaphylaxis and other hypersensitivity reactions have been reported after uneventful test doses as well as therapeutic doses of Iron Dextran Injection, administration of subsequent test doses during therapy should be considered. (See DOSAGE & ADMINISTRATION).

Epinephrine should be immediately available in the event of acute hypersensitivity reactions. The usual adult dose of epinephrine is 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 Iron Dextran Injection.

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*.

Drug/Laboratory Test Interactions: Large doses of Iron Dextran Injection (5 ml or more) have been reported to give a brown colour to serum when blood samples are drawn 4 hours after administration. Iron Dextran Injection may cause falsely elevated serum bilirubin values and falsely decreased serum calcium values. Serum iron determinations (especially by colorimetric assays) may not be meaningful for 3 weeks following administration of Iron Dextran Injection. Serum ferritin peaks approximately 7 to 9 days after an intravenous dose and slowly returns to baseline after about 3 weeks. Examination of bone marrow for iron stores may not be meaningful for prolonged periods following therapy with Iron Dextran Injection because residual iron dextran may remain in reticuloendothelial cells. Bone scans involving ^{99m}Tc-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 iron dextran. In the presence of high serum ferritin levels or following iron dextran infusions, bone scans with

^{99m}Tc-labelled bone seeking agents have been reported to show reduction of bony uptake, marked renal activity, and increased blood pool activity and soft tissue accumulation.

Carcinogenesis, Mutagenesis, Impairment of Fertility: see WARNINGS

Use in Pregnancy: Iron dextran has been shown to be teratogenic and embryocidal in non-anemic 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 have 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 after 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. **Iron Dextran Injection should be used in pregnant women only if the potential benefit justifies the potential risk to the fetus.**

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

Use in Nursing Mothers: Caution should be exercised when Iron Dextran Injection is administered to nursing mothers. Traces of unmetabolized iron dextran are excreted in human milk.

Use in Children: 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 occasion these reactions have been fatal. Such reactions, which occur most often within the first several minutes of administration, are 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 WARNINGS and PRECAUTIONS).

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

Dermatologic: urticaria, pruritus, purpura, rash.

Gastrointestinal: abdominal pain, nausea, vomiting, diarrhea.

Haematologic/Lymphatic: leucocytosis, lymphadenopathy.

Musculoskeletal/Soft Tissue: arthralgia, myalgia, backache, arthritis (may represent reactivation in patients with quiescent rheumatoid arthritis - see PRECAUTIONS); sterile abscess, atrophy/fibrosis, brown skin or underlying tissue discoloration or staining, soreness or pain at or near intramuscular injection sites; cellulitis, swelling, inflammation, local phlebitis at or near intravenous injection sites.

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

Respiratory: respiratory arrest, dyspnea, bronchospasm.

Urologic: haematuria.

Delayed Reactions: arthralgia, backache, chills, dizziness, fever, headache, malaise, myalgia, nausea, vomiting (see WARNINGS).

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

The administration of Iron Dextran Injection has been reported to cause fever and exacerbation of joint pain and swelling in patients with rheumatoid arthritis, ankylosing spondylitis, and systemic lupus erythematosus. (See PRECAUTIONS).

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffectSM Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

OVERDOSAGE

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Overdosage with Iron Dextran Injection is unlikely to be associated with any acute manifestations. Excessive doses beyond the requirements for restoration of haemoglobin and replenishment of iron stores may lead to haemosiderosis. Periodic monitoring of serum ferritin levels may be helpful in recognizing a deleterious progressive accumulation of iron. This can occur when uptake of iron from the reticuloendothelial system is impaired, for example, in chronic renal failure, Hodgkins disease and rheumatoid arthritis.

DOSAGE AND ADMINISTRATION

Oral iron should be discontinued prior to administration of DexIron.

DOSAGE:

I. *Iron Deficiency Anemia:* Periodic determination of haemoglobin and haematocrit is a simple and accurate technique for monitoring haematological response, and should be used as a guide to therapy. It should be noted that iron storage may lag behind the appearance of normal blood morphology. Total iron binding capacity (TIBC), transferrin saturation and serum ferritin are other important tests for detecting and monitoring the iron deficient state. Serum ferritin is generally regarded as the most reliable marker of body iron stores; ie, low serum ferritin correlates closely with low bone marrow iron stores, except in chronic renal dialysis patients who are receiving iron dextran. Serum iron is the least sensitive indicator of the response to Iron Dextran Injection.

After administration of Iron Dextran Injection, evidence of a therapeutic response can be seen in a few days as an increase in the reticulocyte count.

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 haemoglobin 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 haemoglobin. It should be remembered that iron deficiency anemia will not appear until essentially all iron stores have been depleted. Thus, therapy should aim at not only the restoration of haemoglobin but also the

replenishment of iron stores.

Factors contributing to the formula include:

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

- a) Blood volume..... 65 ml/kg of body weight
- b) Normal haemoglobin (males and females)
 - over 15 kg (33 lbs)..... 14.8 g/100 ml
 - 15 kg (33 lbs) or less..... 12 g/100 ml
- c) Iron content of haemoglobin..... 0.34%
- d) Haemoglobin deficit
- e) Weight

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

Note: The formula and accompanying table 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 DEXIRON™ REQUIREMENT FOR HAEMOGLOBIN
RESTORATION AND IRON STORES REPLACEMENT***

Patient Lean Body Weight		Millilitre Requirement of DexIron™ Based On Observed Haemoglobin 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
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 haemoglobin of 14.8 g/dl for body weights greater than 15 kg (33 lbs) and a haemoglobin of 12.0 g/dl for body weights less than or equal to 15 kg (33 lbs).

The total amount of DexIron in ml required to treat anemia and replenish iron stores may be approximated as follows:

For adults and children over 15 kg (33 lbs): See Dosage Table. Alternatively the total dose may be calculated as follows:

$$\text{Dose (ml)} = 0.0442 (\text{Desired Hb} - \text{Observed Hb}) \times \text{LBW} + (0.26 \times \text{LBW})$$

Where, Desired Hb = the target haemoglobin in g/dl.
Observed Hb = the patient's current haemoglobin 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 used to determine the dose.

To convert the patient's weight from pounds to kg:

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

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.

Children 5 to 15 kg (11 to 33 pounds): DexIron should not normally be given in the first four months of life (see PRECAUTIONS). See Dosage Table. Alternatively the total dose may be calculated as follows:

$$\text{Dose (ml)} = 0.0442 (\text{Desired Hb} - \text{Observed Hb}) \times W + (0.26 \times W)$$

Where, Desired Hb = the target haemoglobin in g/dl. (Normal haemoglobin for children weighing 15 kg or less is 12 g/dl).
Observed Hb = the patient's current haemoglobin in g/dl.
W = weight in kg.

To convert the patient's weight from pounds to kg:

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

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 haemorrhagic diatheses (familial telangiectasia, haemophilia, gastrointestinal bleeding) and on a repetitive basis from procedures such as renal dialysis.

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 haematocrit during the bleeding episode provide a convenient method for calculating 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:

$$\text{Replacement iron (in mg)} = \text{Blood loss (in ml)} \times \text{haematocrit}$$

Example: Blood loss of 500 ml with 20% haematocrit

$$\text{Replacement iron} = 500 \times 0.20 = 100 \text{ mg}$$

$$\text{DexIron dose} = \frac{100 \text{ mg}}{50 \text{ mg/ml}} = 2 \text{ ml}$$

ADMINISTRATION:

The total amount of DexIron required for the treatment of iron deficiency anemia or iron replacement for blood loss is determined from the table or appropriate formula (see DOSAGE).

1. Intravenous Injection - PRIOR TO RECEIVING THEIR FIRST DEXIRON THERAPEUTIC DOSE, ALL PATIENTS SHOULD BE GIVEN AN INTRAVENOUS TEST DOSE OF 0.5 ML. (See PRECAUTIONS). THE TEST DOSE SHOULD BE ADMINISTERED AT A GRADUAL RATE OVER AT LEAST 5 MINUTES.

Although anaphylactic reactions known to occur following administration of Iron Dextran Injection are usually evident within a few minutes or sooner, it is recommended that a period of 1 hour or longer elapse before the remainder of the initial therapeutic dose is given.

Because anaphylaxis and other hypersensitivity reactions have been reported after uneventful test doses as well as therapeutic doses of Iron Dextran Injection, administration of subsequent test doses during therapy should be considered (see PRECAUTIONS).

Individual doses of 2 ml or less may be given on a daily basis until the calculated total amount required has been reached. DexIron is given undiluted at a **slow gradual rate** not to exceed 50 mg (1 ml) per minute. Monitor patients for signs and symptoms of hypersensitivity during and after DexIron administration for at least 30 minutes and until clinically stable following the injection.

2. Intramuscular Injection - PRIOR TO RECEIVING THEIR FIRST DEXIRON THERAPEUTIC DOSE, ALL PATIENTS SHOULD BE GIVEN AN INTRAMUSCULAR TEST DOSE OF 0.5 ML GRADUALLY. (See PRECAUTIONS). The test dose should be administered in the same recommended test site and by the same technique as described in the last paragraph of this section.

Although anaphylactic reactions known to occur following administration of Iron Dextran Injection are usually evident within a few minutes or sooner, it is recommended that a period of 1 hour or longer elapse before the remainder of the initial therapeutic dose is given.

Because anaphylaxis and other hypersensitivity reactions have been reported after uneventful test doses as well as therapeutic doses of Iron Dextran Injection, administration of subsequent test doses during therapy should be considered (see PRECAUTIONS)."

If no adverse reactions are observed, DexIron 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. Monitor patients for signs and symptoms of hypersensitivity during and after DexIron administration for at least 30 minutes and until clinically stable following the injection.

DexIron 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 5 cm (2-inch or 3-inch), 19 or 20 gauge needle. In an obese patient, a longer needle is usually necessary, and in children and frail adults a shorter and smaller needle will suffice. If the patient is standing, he/she should be bearing his/her weight on the leg opposite the injection site. If recumbent, he/she should be in the lateral position with the injection site uppermost. To avoid injection or leakage into the subcutaneous tissue, a Z-track technique (lateral displacement of the skin prior to injection) is recommended.

The intramuscular route of administration is to be used unless there are valid reasons for intravenous administration.

NOTE: Do not mix DexIron 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.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper (Common) Name: Iron Dextran
Chemical Name: Iron Dextran
Structural Formula: $[\text{Fe}_p\text{O}_r(\text{OH})_s]_L \bullet \{[\text{C}_6\text{H}_{10}\text{O}_5]_m\}_a$

Where:

L = degree of polymerization of $\text{Fe}_p\text{O}_r(\text{OH})_s$ (ferric oxyhydroxide).
For the iron dextran, the number of iron atoms is approximately 900.

m = degree of polymerization of the anhydroglucose unit, $\text{C}_6\text{H}_{10}\text{O}_5$.
For the iron dextran, this value is approximately 30.

a = stoichiometric factor from iron and ligand analysis. For the iron dextran, this value is approximately 15.

Molecular Weight:	Approximately 400,000 daltons
Physical Form:	Powder
Solubility:	Soluble in water. Insoluble in organic solvents.
pK _a :	Not applicable
pH (aqueous solution):	4.5 to 6.5
Partition Coefficient:	Not applicable
Melting Point:	Not applicable, substance decomposes
Description:	Iron dextran is an odourless brown amorphous powder composed of a core of $\beta\text{-FeO}(\text{OH})$ (beta-ferric oxyhydroxide) bound to low molecular weight dextran. The iron core consists of a ferric iron surrounded by six oxygens present as OH^- , O^{2-} , and H_2O . During the polymerization that occurs during manufacture, the core grows in a chain formation, eventually forming a polynuclear, ellipsoid core.

Composition DexIronTM (Iron Dextran Injection, USP) is a dark brown, slightly viscous sterile liquid complex of ferric oxyhydroxide and a low molecular weight dextran.
Each ml contains:
Elemental iron as iron dextran.....50 mg
Water for injection, qs.....1 ml

Sodium chloride, USP may be added to adjust tonicity. Sodium hydroxide, NF (4% v/v solution) and/or hydrochloric acid, NF (10% v/v solution) added as necessary to adjust pH.

Stability and Storage Recommendations

DexIron should be stored at room temperature, 15°-30°C (59°-86°F). Protect from excessive heat. Do not freeze. Keep out of reach of the children.

AVAILABILITY AND DOSAGE FORMS

DexIron™ (Iron Dextran Injection, USP) containing 50 mg of elemental iron per ml, for intramuscular or intravenous injection, is available in 1 ml and 2 ml single dose vials supplied in cartons of 10 vials. Store at controlled room temperature, 15°-30°C (59°-86°F). Protect from excessive heat. Do not freeze. Keep out of the reach of children.

PHARMACOLOGY

Pharmacodynamics

Iron Dextran Injection provides the iron-deficient person with a usable source of iron for erythropoiesis and replacement of body iron stores. Iron dextran does not stimulate erythropoiesis nor does it correct anemia which is not caused by iron deficiency. After intravenous or intramuscular injection, circulating iron dextran is gradually removed from plasma by cells of the reticuloendothelial system, which split the complex into its components of iron and dextran. This occurs primarily in the liver and spleen. Dextran, a polyglucose which serves to stabilize the complex, has no biological importance and is metabolized and excreted. The iron is immediately bound to the available protein moieties to form haemosiderin or ferritin, and to a lesser extent transferrin. In these physiologic forms, the iron is available for haemoglobin synthesis, synthesis of other iron-containing compounds and enzymes, and replenishment of depleted iron stores. The ratio of ferritin to haemosiderin, the two iron-storage compounds, depends on the total body iron content. Ferritin, the major storage form of iron, predominates when total body iron is low. Haemosiderin, the long-term storage compound, predominates when total body iron is high.

Iron is not easily eliminated from the body. The iron which is liberated from the turnover of senescent red blood cells is recycled and reutilized. Urinary and fecal iron losses are minimal. Similarly, negligible amounts of iron are lost via the urinary or alimentary pathways after administration of iron dextran. Body iron balance is regulated by the rate of dietary iron absorption from the upper small intestine. Parenteral administration of iron dextran bypasses this physiological control mechanism since suppression of intestinal absorption cannot compensate

for the amount of iron delivered parenterally. The consequence is that the injudicious use of iron dextran can lead to toxic accumulation of iron in the body, or iron overload. Therefore, Iron Dextran Injection should only be administered in proven states of iron deficiency in patients in whom oral iron replacement therapy is not effective (noncompliance, ulcerative colitis, Crohn's disease, malabsorption, gastric intolerance, severe iron deficiency, patients with end stage renal disease, etc.).

Response to Iron Dextran Injection is rapid, with reticulocytes appearing in the peripheral blood as early as the fourth day after treatment. Maximum response usually occurs within 2 to 3 weeks and then the rate of erythropoiesis decreases gradually. If the patient's haemoglobin fails to increase by approximately 1 g/dl within 2 weeks, the diagnosis of iron deficiency anemia should be reconsidered.

Pharmacokinetics

Absorption

Following intramuscular administration, iron dextran is absorbed from the site of injection primarily through the lymphatic system. Absorption takes place in two stages. Approximately 60% of the dose of iron dextran injected is absorbed within 72 hours of administration. Ninety percent of the dose is absorbed in the second, slower, phase lasting approximately 1 to 3 weeks in duration. The remaining 10% of the dose is gradually absorbed over a period of several months or longer.

There is poor correlation between the degree of anemia and the rate of iron absorption. However, individual variation in absorption from intramuscular injection sites may be related to the level of exercise or activity.

Distribution, Utilization, and Clearance

Iron dextran is detectable in plasma within 3 to 4 hours after intramuscular injection, and reaches peak concentrations in 24 to 48 hours.

After intravenous injection of 2 ml of DexIron (100 mg iron) to renal dialysis patients, maximum serum concentration of iron dextran in the order of $3,400 \pm 1,200$ $\mu\text{g}/\text{dl}$ were observed at 3.4 ± 1.8 hours. The average half-life of iron dextran in serum was 58.9 hours, ranging from 9.4 to 87.4 hours in 20 patients. This study was not conducted with radiolabelled DexIron. The concentration of iron dextran in the serum was calculated as the difference between the total serum iron and the transferrin-bound iron. Thus, direct comparison to results obtained in studies using ^{59}Fe -labelled iron dextran should be avoided. It should be noted that half-lives of iron dextran reflect uptake of the complex by the reticuloendothelial system (RES). Cells of the RES split the iron dextran complex into iron and dextran. While the dextran is subsequently eliminated, the iron is immediately bound to form ferritin, haemosiderin, or transferrin, and is not eliminated from the body.

The availability of iron for erythropoiesis and replenishment of iron stores after administration of DexIron was evaluated in a study of 20 renal dialysis patients. A total dose equivalent to 500 mg of iron, divided into five 100 mg doses was administered intravenously over a period of 10 days. (The dosing schedule varied according to the patient's clinical situation). Haemoglobin increased from a pre-treatment mean of 10.3 g/dl to 11.4 g/dl two weeks after completion of the series of injections. Serum ferritin and transferrin saturation peaked in one week at 620 ng/ml and 32%, respectively. Total iron binding capacity remained well within the physiological range (245-400 µg/dl) for the duration of the 30 day observation period, an indication that free ionic iron is not released from iron dextran. The mean product utilization of iron from Dextran was calculated to be $47 \pm 20\%$.

TOXICOLOGY

Acute Toxicity

The toxicity of Iron Dextran Injection is very low; the intravenous LD₅₀ is not less than 500 mg/kg in the mouse. Other routes of administration may be associated with an LD₅₀ of more than 1000 mg/kg. The low toxicity of Iron Dextran is due to the stability of the iron dextran complex. The iron dextran complex contains no ionic iron, which is responsible for the well-characterized signs of iron poisoning that appear after an oral overdose of a ferrous salt.

Subacute and Chronic Toxicity

The long-term toxicity of iron dextran has been investigated in several species after intramuscular and intravenous injection, and over a wide range of doses.

Rats treated with iron dextran by intramuscular injection at a total dose of 100 mg of iron/kg in divided doses over a 12-week period exhibited no drug-related abnormalities. At ten times this dose, 1000 mg of iron/kg, treated rats had enlarged livers and spleens compared to control rats. In a 12 week study in rabbits treated with iron dextran equivalent to a total dose 1060 mg of iron/kg intramuscularly, considerable deposits of iron were seen in histological sections of muscle fibers at injection sites. No significant toxic effects or pathologic changes were observed when iron dextran was administered intravenously in doses equivalent to 5 mg of iron/kg to rabbits weekly for 10 weeks. Severe renal damage was observed when the experiment was repeated using a dose of 50 mg of iron/kg. Mice, rats, and guinea pigs treated with dosages as high as 30 times the clinical dose and followed for more than one year showed no ill effects.

Massive doses of iron dextran have been associated with the development of sarcomata at intramuscular injections sites in some animal species (rodents, rabbits, but not dogs or guinea pigs). Lower doses are not associated with carcinogenesis unless intramuscular injections are repeatedly administered into a single site. There is no evidence that intramuscular injection of iron dextran

carries a serious risk of tumor development in humans. In the few documented cases of sarcomata at iron dextran intramuscular injection sites in man, a causal relationship was not established in each patient.

The most common manifestation of excessive iron dextran administration in man is iron overload or haemosiderosis. This is most likely to occur when iron deficiency anemia has been misdiagnosed and in patients receiving numerous blood transfusions in addition to iron dextran therapy. While physiological haemosiderosis is not associated with tissue damage, extreme iron overload can lead to cardiac, hepatic, and endocrine abnormalities, and defects in cell-mediated immunity.

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