1. NAME OF THE MEDICINAL PRODUCT

Brand Name: DEXTRAN

Generic Name: Iron Dextran Injection BP 50mg/ml

Composition:
Each ml contains
Iron Dextran Equivalent to elemental Iron..... 50 mg
Water for Injections BP..... QS

Pharmaceutical form: Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Batch Size: 90196 Nos / 460Lts

SR. No	Ingredients	Specification	Composition	Overages	Qty per ml	Qty/ Batch size	Rationale
	ACTIVE						
1.	Iron dextran	INH	50 mg	--	50mg	60.210kg	Active
	EXCIPIENTS						
2.	Sodium chloride BP	BP	0.9%w/v	--	9.0mg	4.140kg	Tonicity
3.	Water for Injections	BP	q.s	--	Qs to 1ml	460lts	Solvent

Where, BP- British Pharmacopoeia , q.s.- quantity sufficient

3. PHARMACEUTICAL FORM

Solution for Injection

4. Clinical particulars

4.1 Therapeutic indications

Heamatinic

For adults only
Iron dextran is indicated for the treatment of iron deficiency in the following indications:
•When oral iron preparations cannot be used, e.g. due to intolerance, or in case of demonstrated lack of effect of oral iron therapy
•Where there is a clinical need to deliver iron rapidly to iron stores.
The diagnosis of iron deficiency must be based on appropriate laboratory tests (e.g. Serum ferritin, serum iron, transferrin saturation and hypochromic red cells).

4.2 Posology and method of administration

Monitor carefully patients for signs and symptoms of hypersensitivity reactions during and following each administration of Iron dextran.
Iron dextran should only be administered when staff trained to evaluate and manage anaphylactic reactions is immediately available, in an environment where full resuscitation facilities can be assured. The patient should be observed for adverse effects for at least 30 minutes following each Iron dextran injection (see section 4.4).

Administration:

Iron dextran solution for infusion and injection can be administered by an intravenous drip infusion or by a slow intravenous injection of which the intravenous drip infusion is the preferred route of administration, as this may help to reduce the risk of hypotensive episodes. However, Iron dextran may also be administered as undiluted solution intramuscularly.

Adults and elderly

The total cumulative dose of Iron dextran is determined by haemoglobin level and body weight. The dose and dosage schedule for Iron dextran must be individually estimated for each patient based on a calculation of the total iron deficit.

Children (under 14 years)

Iron dextran should not be used for children. There is no documentation for efficacy and safety.

Dosage:

The normal recommended dosage schedule is 100-200 mg iron corresponding to 2-4 ml, two or three times a week depending on the haemoglobin level. However, if clinical circumstances require rapid delivery of iron to the body iron stores Iron dextran may be administered as a total dose infusion up to a total replacement dose corresponding to 20 mg iron/kg body weight.
The Iron dextran injection should not be administered concomitantly with oral iron preparations as the absorption of oral iron will be reduced (please refer to section 4.5).

Intravenous drip infusion:

Iron dextran must be diluted only in 0.9% sodium chloride solution (normal saline) or in 5% glucose solution. Iron dextran in a dose of 100-200 mg iron (2-4ml) may be diluted in 100 ml. On each occasion the first 25 mg of iron should be infused over a period of 15 minutes. If no adverse reactions occur during this time the remaining portion of the infusion should be given at an infusion rate of not more than 100 ml in 30 minutes.

Intravenous injection:

Iron dextran may be administered in a dose of 100 – 200 mg iron (2-4 ml) by slow intravenous injection (0.2 ml/min) preferably diluted in 10 – 20 ml 0.9% sodium chloride or 5% glucose solution. On each occasion before administering a slow intravenous injection, 25 mg of iron should be injected slowly over a period of 1 to 2 minutes. If no adverse reactions occur within 15 minutes, the remaining portion of the injection may be given.

Total dose infusion:

Immediately before administration the total amount of Iron dextran required, determined from the dosage table or by calculation, is added aseptically to the required volume, usually 500 ml of sterile normal sodium chloride or 5% glucose solutions. The total amount of Iron dextran, up to 20 mg/kg bodyweight, is infused intravenously over 4 – 6 hours. The first 25 mg of iron should be infused over a period of 15 minutes. The patient must be kept under close medical observation during this period. If no adverse reactions occur during this time, then the remaining portion of the infusion should be given. The rate of infusion may be increased progressively to 45 – 60 drops per minute. Patients should be observed carefully during the infusion and for at least 30 minutes after completion.
Total Dose Infusion (TDI) has been associated with an increased incidence of adverse reactions, in particular delayed hypersensitivity–like reactions. The intravenous administration of Iron dextran by the total dose infusion method should be restricted to hospital use only.

Injection into dialyser:

Iron dextran may be administered during a haemodialysis session directly into the venous limb of the dialyser under the same procedures as outlined for intravenous administration.

Intramuscular injection:

The total amount of Iron dextran required is determined either from the dosage table or by calculation. It is

administered as a series of undiluted injections of up to 100 mg iron (2.0 ml) each determined by the patient's body weight. If the patient is moderately active, injections may be given daily into alternate buttocks. In inactive or bedridden patients, the frequency of injections should be reduced to once or twice weekly.
Iron dextran must be given by deep intramuscular injection to minimise the risk of subcutaneous staining. It should be injected only into the muscle mass of the upper outer quadrant of the buttock - never into the arm or other exposed areas. A 20 - 21 gauge needle at least 50 mm long should be used for normal adults. For obese patients the length should be 80
100 mm whereas for small adults a shorter and smaller needle (23 gauge x 32 mm) is used. The patient should be lying in the lateral position with the injection site uppermost, or standing bearing their weight on the leg opposite the injection site. To avoid injection or leakage into the subcutaneous tissue, a Z-track technique (displacement of the skin laterally prior to injection) is recommended. Iron dextran is injected slowly and smoothly. It is important to wait for a few seconds before withdrawing the needle to allow the muscle mass to accommodate the injection volume. To minimise leakage up the injection track, the patient should be encouraged not to rub the injection site.

Calculation of dose:

a) Iron replacement in patients with iron deficiency anaemia:

Factors contributing to the formula are shown below. The required dose has to be individually adapted according to the total iron deficit calculated by the following formula haemoglobin in g/l or mmol/l.

Total dose (mg Fe) – Hb in g/l:

(Body weight (kg) x (target Hb - actual Hb) (g/l) x 0.24) + mg iron for iron stores

The factor 0.24 is derived from the following assumptions:

a) Blood volume 70 ml/kg of body weight ≈ 7% of body weight

b) Iron content of haemoglobin 0.34%

Factor 0.24 = 0.0034 x 0.07 x 1000 (conversion from g to mg).

Total dose (mg Fe) – Hb in mmol/l:

Body weight in kg x (target Hb in mmol/l – actual Hb in mmol/l) x 3.84 + mg iron for iron stores.

The factor 3.84 is derived from the following assumptions:

a) Blood volume 70 ml/kg of body weight ≈ 7% body weight

b) Iron content of haemoglobin 0.34%

c) Factor for conversion from haemoglobin g/l to mmol/lis

0.06205 Factor 3.84 = 0.0034 x 0.07 x 1000 / 0.06205

The table below shows the number of millilitres of Iron dextran injection solution to be used at various degrees of iron deficiency anaemia.

The figures in the table below are based on a target haemoglobin of 150 g/l or 9.3 mmol/l and iron stores of 500 mg which apply to a body weight exceeding 35 kg.

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 anaemia will not appear until essentially all iron stores have been depleted. Therapy, thus, should aim at not only replenishment of haemoglobin iron but of iron stores as well.

If the total necessary dose exceeds the maximum allowed daily dose, the administration has to be split. Evidence of a therapeutic response can be seen within a few days of administration of Iron dextran as an increase in the reticulocyte count. Serum ferritin levels usually provide a good guide to the replenishment of iron stores. In renal dialysis patients receiving Iron dextran, this correlation may not be valid.

Total dose of Iron dextran in Millilitres to be administered in iron deficiency anaemia

Haemoglobin content Body weight (kg)	60 g/l ≈ 3.7 mmol/l	75 g/l ≈ 4.7 mmol/l	90 g/l ≈ 5.6 mmol/l	105 g/l ≈ 6.5 mmol/l	120 g/l ≈ 7.4 mmol/l	135 g/l ≈ 8.4 mmol/l
35	25	23	20	18	15	12.5
40	27	24	22	19	16	13
45	29	26	23	20	16.5	13
50	32	28	24	21	17	13.5
55	34	30	26	22	18	14
60	36	32	27	23	18.5	14.5
65	38	33	29	24	19.5	14.5
70	40	35	30	25	20	15
75	42	37	32	26	21	15.5
80	45	39	33	27	21.5	16
85	47	41	34	28	22	16
90	49	42	36	29	23	16.5

Note: The table and accompanying formula are applicable for dose determination only in patients with iron deficiency anaemia. They are not to be used for dose determination in patients requiring iron replacement for blood loss.
b) Iron replacement for blood loss:
Iron therapy in patients with blood loss should be directed toward replacement of an amount of iron equivalent to the amount of iron represented in the blood loss. The table and formula described 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 of calculation of the required iron dose.
The required Iron dextran dose to compensate the iron deficit is calculated according to the following formulas:
-If the volume of blood lost is known: The administration of 200 mg i.v. iron (4 ml Iron dextran) results in an increase of haemoglobin which is equivalent to 1 unit blood (= 400 ml with 150 g/l Hb content or 9.3 mmol Hb/l – equivalent to 0.34% of 0.4 x 150 or 204 mg iron).
Iron to be replaced [mg] = number of blood units lost x 200. Millilitres of Iron dextran needed = number of blood units lost x 4.
-If the Hb level is reduced: Use the previous formula considering that the depot iron does not need to be restored.
Mg iron to be replaced = body weight (kg) x 0.24 x (target Hb in g/l - actual Hb in g/l). Or
E.g.: body weight 60 kg, Hb deficit = 10 g/l or 0.62 mmol/l:
Iron to be replaced = 60 x 0.24 x 10 = 60 x 3.84 x 0.62 = 143 mg (≈ 3 millilitres Iron dextran)

4.3 Contraindications

Hypersensitivity to the active substance, to Iron dextran or any of its excipients listed in section 6.1.

Known serious hypersensitivity to other parenteral iron products. Non-iron deficiency anaemia

(e.g. haemolytic anaemia).

Iron overload or disturbances in utilisation of iron (e.g. haemochromatosis, haemosiderosis).

Decompensated liver cirrhosis and hepatitis.

Acute or chronic infection, because parenteral iron administration may exacerbate bacterial or viral infections.
Acute renal failure

4.4 Special warnings and precautions for use

Parenterally administered iron preparations can cause hypersensitivity reactions including serious and potentially fatal anaphylactic/anaphylactoid reactions. Hypersensitivity reactions have also been reported after previously uneventful doses of parenteral iron complexes. There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction, see section 4.8).

The risk is enhanced for patients with known allergies including drug allergies, including patients with a history of severe asthma, eczema or other atopic allergy.

There is also an increased risk of hypersensitivity reactions to parenteral iron complexes in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis).

Iron dextran should only be administered when staff trained to evaluate and manage anaphylactic reactions is immediately available, in an environment where full resuscitation facilities can be assured. Each patient should be observed for adverse effects for at least 30 minutes following each Iron dextran injection. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Facilities for cardio respiratory resuscitation and equipment for handling acute anaphylactic/anaphylactoid reactions should be available, including an injectable 1:1000 adrenaline solution. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.
The intramuscular and subcutaneous injection of iron-carbohydrate complexes in very large doses under experimental conditions in animals produced sarcoma in rats, mice, rabbits possibly hamsters but not in guinea pigs. Cumulative information and independent assessment indicate that the risk of sarcoma formation in man is minimal.
Hypotensive episodes may occur if intravenous injection is administered too rapidly.

4.5 Interaction with other medicinal products and other forms of interaction

The Iron dextran injection should not be administered concomitantly with oral iron preparations as the absorption of oral iron will be reduced. Oral iron therapy should not be started earlier than 5 days after the last injection of Iron dextran.
Large doses of iron dextran (5 ml or more) have been reported to give a brown colour to serum from a blood sample drawn four hours after administration.
The drug may cause falsely elevated values of serum bilirubin and falsely decreased values of serum calcium

4.6 Pregnancy and Lactation

There are no adequate and well-controlled trials of Iron dextran in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). A careful risk/benefit evaluation is therefore required before use during pregnancy and Iron dextran should not be used during pregnancy unless clearly necessary (see section 4.4).

Iron deficiency anaemia occurring in the first trimester of pregnancy can in many cases be treated with oral iron. Treatment with Iron dextran should be confined to second and third trimester if the benefit is judged to outweigh the potential risk for both the mother and the foetus.

Foetal bradycardia may occur following administration of parenteral irons. It is usually transient and a consequence of a hypersensitivity reaction in the mother. The unborn baby should be carefully monitored during intravenous administration of parenteral irons to pregnant women.

It is unknown whether the complex iron-dextran is excreted in human or animal breast milk. It is preferable to not use Iron dextran during breast-feeding

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed

4.8 Undesirable effects

Approximately 5% of patients can be expected to experience adverse reactions. These are mainly dose dependent.

Anaphylactoid reactions are uncommon and include urticaria, rashes, itching, nausea and shivering. Administration must be stopped immediately when signs of an anaphylactoid reaction are observed.

Acute, severe anaphylactoid reactions are very rare. They usually occur within the first few minutes of administration and are generally characterised by the sudden onset of respiratory difficulty and / or cardiovascular collapse; fatalities have been reported.

Delayed reactions are well described and may be severe. They are characterised by arthralgia, myalgia and sometimes fever. The onset varies from several hours up to four days after administration. Symptoms usually last two to four days and settle spontaneously or following the use of simple analgesics.

Exacerbation of joint pain in rheumatoid arthritis can occur. Local reactions reported are soreness and inflammation at or near injection site and local phlebitic reaction.

Local complications at the injection site after intramuscular injection such as staining of the skin, bleeding, formation of sterile abscesses, tissue necrosis or atrophy and pain are observed.

Organ System	**Uncommon** (>1/1,000, <1/100)	**Rare** (>1/10,000, <1/1,000)	***Very rare*** <1/10,000	**Not known**
Blood and lymphatic system disorders			Haemolysis	
Cardiac disorders		Arrythmia, tachycardia	Foetal bradycardia, palpitations	Kounis syndrome
Ear and labyrinth disorders			Transient deafness	
Gastrointestinal disorders	Nausea, emesis, abdominal pain	Diarrhoea		
General disorders and administration site conditions	Feeling hot	Fatigue Pain and brown pigmentation at injection site		Influenza like illness whose onset may vary from a few hours to several days
Immune system disorders	Anaphylactoid reactions including dyspnoea, urticaria, rashes, itching, nausea and shivering		Acute, severe anaphylactoid reactions (sudden onset of respiratory difficulty and / or cardiovascular collapse)	
Musculoskeletal and connective tissue disorders	Cramps	Myalgias		

Nervous system disorders	Blurred vision, numbness	Loss of consciousness, seizure, dizziness, restlessness, tremor	Headache, paresthesia	
Respiratory, thoracic and mediastinal disorders	Dyspnea	Chest pain		
Psychiatric disorders		Mental status changes		
Skin and subcutaneous tissue disorders	Flushing, pruritus, rash	Angioedema, Sweating		
Vascular disorders		Hypotension	Hypertension	

4.9 Overdose

Iron(III)-hydroxide dextran complex in Iron dextran injection has a very low toxicity. The preparation is well tolerated and has a minimal risk of accidental overdosing.
Overdose can cause acute iron overloading which may manifest itself as haemosiderosis. Supportive measures such as iron chelating agent can be used.
With chronic repeated administration of iron at high dose, the excess iron will accumulate in the liver and induce an inflammatory process, which may lead to fibrosis

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties Pharmacotherapeutic group: Heamatinic,

ATC code: B03AC

Iron dextran solution for infusion and injection contains iron as a stable iron(III)-hydroxide dextran complex, which is analogous to the physiological form of iron, ferritin (ferric hydroxide phosphate protein complex). The iron is available in a non-ionic water-soluble form. It has a very low toxicity and can be given in large doses.

Serum ferritin peaks approximately 7 to 9 days after an intravenous dose of Iron dextran and slowly returns to baseline 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

5.2 Pharmacokinetic properties

Following the i.v. infusion the iron dextran is rapidly taken up by the cells in the reticuloendothelial system (RES), particularly in the liver and spleen from where iron is slowly released and bound to proteins. After administration an increased hematopoiesis can be observed for the next 6-8 weeks. The plasma half life is 5 hours for circulating iron and 20 hours for total iron (bound and circulating).

Circulating iron 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 haemoglobin and depleted iron stores.

Iron is not easily eliminated from the body and accumulation can be toxic. Due to the size of the complex (165,000 Daltons) it is not eliminated via the kidneys. Small quantities of iron are eliminated in urine and faeces.

After intramuscular injection, iron dextran is absorbed from the injection site into the capillaries and the lymphatic system. The major portion of the intramuscularly administered iron dextran is absorbed within 72 hours; most of the remaining iron is absorbed during the ensuing 3 to 4 weeks.

Dextran is either metabolised or excreted.

5.3 Preclinical safety data

Iron dextran has been reported to be teratogenic and embryocidal in non-anaemic pregnant animals at high single doses above 125 mg/kg. The highest recommended dose in clinical use is 20 mg/kg. However, no detailed information is available from these studies.
In vitro and in vivo genotoxicity studies have showed mutagenic activity after the administration of high doses of iron-dextran complexes. However the significance of these results is not clear. Iron dextran was not mutagenic at sub-toxic dose levels.
There are no other additional preclinical data of relevance to the prescriber than those already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride BP
Water For Injections BP

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

6.3 Shelf life

24 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. Do not freeze

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

5ml X 100 Ampoules packed in carton along with leaflet.

6.6 Special precautions for disposal <and other handling>

No special requirements

7. <APPLICANT >

MacDech Pharm Co. Ltd.
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