Further information concerning the dosage of iron salts and compounds used is provided in the individual monographs; this information, however, tends to reflect the amounts of iron contained in different salts or available commercial preparations and therefore, in some instances, may not be within the general range of iron dosages as quoted above.

The iron content of various iron salts is tabulated in Table 1, below.

Modified-release dosage forms of iron are claimed to result in reduced gastrointestinal adverse effects and have the advantage of once-daily dosage. The preparations are designed to release the iron gradually along the gut but in some instances the iron may not be released until the preparation reaches a part of the gut where absorption is poor thus resulting in sub-optimal dosing.

Iron can also be given parenterally in circumstances where oral therapy cannot be undertaken and such use is typified by iron dextran (see p.1951).

Administration in the elderly. Patients over 80 years of age with iron-deficiency anaemia (below) were randomised to elemental iron therapy in daily doses of 15 mg, 50 mg (as liquid ferrous gluconate), or 150 mg (as tablets of calcium ferrous citrate) and treated for 2 months.[1] Serum haemoglobin and ferritin concentrations increased significantly in all patients, without significant differences between the 3 doses. The authors concluded that, while these results may not apply to patients with iron deficiency due to malabsorption, chronic disease, or untreated *Helicobacter pylori* infection, low-dose therapy is an effective option for elderly patients with iron-deficiency anaemia, in whom the adverse effects of iron could cause considerable morbidity and impaired compliance. Younger patients could also probably be treated effectively with low-dose iron therapy.

1. Rimon E, *et al.* Are we giving too much iron? Low-dose iron therapy is effective in octogenarians. *Am J Med* 2005; **118:** 1142–7.

Anoxic seizures. Reductions in the frequency of breath-holding episodes in children treated with iron,[1] and especially in those with iron-deficiency anaemia,[2,3] suggest that there might be a relationship between anoxic seizures (p.1221) and iron deficiency.[4]

1. Daoud AS, *et al.* Effectiveness of iron therapy on breath-holding spells. *J Pediatr* 1997; **130:** 547–50.
2. Mocan H, *et al.* Breath holding spells in 91 children and response to treatment with iron. *Arch Dis Child* 1999; **81:** 261–2.
3. Pedersen KW, Knudsen FU. Skal børn med affektkramper behandles med jern? *Ugeskr Laeger* 2004; **166:** 2789–91.
4. Hannon DW. Breath-holding spells: waiting to inhale, waiting for systole, or waiting for iron therapy? *J Pediatr* 1997; **130:** 510–12.

Cough. In a small study[1] of 19 patients, iron supplementation with ferrous sulfate successfully reduced the cough associated with ACE inhibitors (see p.1194). The authors hypothesised that this effect was due to the inhibition by iron of nitric oxide synthase. However, there are some concerns[2] about the effect of giving a nitric oxide synthase inhibitor to hypertensive patients, as it has been found to increase blood pressure in *animal* studies.

1. Lee S-C, *et al.* Iron supplementation inhibits cough associated with ACE inhibitors. *Hypertension* 2001; **38:** 166–70.
2. Lev I, Rian AJJT. Iron supplementation in ACE inhibition as a treatment for cough: is it really inoffensive? *Hypertension* 2001; **38:** e38.

Iron-deficiency anaemia. The iron content of the body is normally kept constant by regulation of the amount absorbed to balance the amount lost. If loss is increased, and/or intake inadequate, a negative iron-balance may lead by degrees to depletion of body iron stores, iron deficiency, and eventually to anaemia. Iron requirements are increased during infancy, puberty, pregnancy, and during menstruation, and iron-deficiency anaemias are most common in women and children; the most common cause in adult males and postmenopausal women is blood loss, usually from the gastrointestinal tract.

Iron deficiency usually results in a microcytic, hypochromic anaemia, but the diagnosis of iron deficiency should be confirmed, if there is any doubt, by measurement of serum ferritin, erythrocyte protoporphyrin, or total iron binding capacity (transferrin). Iron therapy can begin once deficiency is confirmed, but the underlying cause of the deficiency should still be sought and treated.

Table 1. Approximate amounts of different iron salts that supply 60 mg of elemental iron.

Iron salt	Amount
Ferrous ascorbate (anhydrous)	437 mg
Ferrous aspartate (tetrahydrate)	422 mg
Ferrous chloride (tetrahydrate)	214 mg
Ferrous fumarate (anhydrous)	183 mg
Ferrous gluconate (dihydrate)	518 mg
Ferrous succinate (anhydrous)	185 mg
Ferrous sulfate (dried)	186 mg
Ferrous sulfate (heptahydrate)	300 mg

Treatment. The prevention and control of iron-deficiency anaemias has been reviewed.[1-4] Almost all iron-deficiency anaemias respond readily to treatment with iron. The treatment of choice is an oral ferrous salt (ferrous iron is better absorbed than ferric iron).[1] Many iron compounds have been used for this purpose, but do not offer any real advantage over the simple ferrous fumarate, gluconate, or sulfate salts. The usual adult dose is sufficient of these salts to supply about 100 to 200 mg of elemental iron daily (for the elemental iron content of various iron salts, see above), with the aim of increasing haemoglobin concentrations by about 1 g/litre daily or about 20 g/litre every 3 weeks.[1] Haemoglobin response is greatest in the first few weeks of therapy and is proportional to the severity of the original anaemia. Once haemoglobin concentrations have risen to the normal range, iron therapy should be continued for a further 3 months to aid replenishment of iron stores.[1,3] For the view that low-dose iron therapy may be as effective as higher doses, see Administration in the Elderly, above.

Oral iron has been given with agents such as ascorbic acid to enhance iron absorption, and modified-release preparations have been used in patients intolerant of ordinary formulations of iron but the *BNF* considers them to have no therapeutic advantage.

Failure to respond to oral iron after about 3 weeks of therapy may be indicative of non-compliance, continued blood loss with inadequate replacement of iron, malabsorption, wrong diagnosis, or other complicating factors, and the treatment should be reassessed.

Parenteral iron therapy is rarely indicated, may produce severe adverse effects, and should be reserved for patients who are genuinely intolerant of oral iron, persistently non-compliant,[3] who have gastrointestinal disorders exacerbated by oral iron therapy, continuing blood loss too severe for oral treatment to provide sufficient iron, or for those unable to absorb iron adequately from the gastrointestinal tract. Patients with chronic renal failure on haemodialysis (and some on peritoneal dialysis) require regular iron. US guidelines[5] suggest that intravenous use is preferred in haemodialysis patients, but that iron may be given either intravenously or orally in predialysis and peritoneal dialysis patients. The most common parenteral forms are iron dextran, iron sorbitol, iron sucrose, and sodium ferric gluconate complex.

Exceptionally, in patients with profound anaemia, blood transfusion may be necessary to restore dangerously low concentrations of haemoglobin. This may be the case, for example, in cases of worsening angina or severe coexisting pulmonary disease.[1] However, transfusion should always be avoided if possible.

Prophylaxis. Prophylaxis may be desirable in some groups at risk of iron deficiency and consequent anaemia, and may include therapy with oral iron supplements, measures to improve dietary iron intake, fortification of food staples, or control of infection. For the possible problems associated with iron supplementation in those who are not deficient, see Effects in Non-deficient Subjects, under Precautions, above.

WHO[2] recommends that universal supplementation of iron and folic acid should be implemented for pregnant women, starting as soon as possible after gestation starts and continuing for the rest of the pregnancy. WHO also recommends that where anaemia prevalence is above 40%, women of child-bearing age and lactating women should be given 3 months of iron and folic acid supplementation. However, the US Preventive Services Task Force has reviewed the subject of iron supplementation during pregnancy,[6] and concluded that there was insufficient evidence for or against routine supplementation.[7]

Iron supplementation is accepted in menorrhagia, after gastrectomy, and in the management of low birth-weight infants such as the premature. Iron deficiency in infants and children may result in developmental delay or impairment of cognitive function.[2] Breast feeding should be encouraged during the first year of life.[1] WHO has suggested[2] that low birth-weight infants be given universal supplementation. Where the diet does not include foods fortified with iron or where anaemia prevalence is above 40%, iron supplementation should be given to all children between 6 and 23 months of age; for children aged 24 months and above, a 3-month course of iron supplementation should be given where the anaemia prevalence is above 40%.

The usual prophylactic dose in adults suggested by WHO is about 60 mg of elemental iron daily. Doses of about 2 mg/kg of elemental iron daily (up to 30 mg) have been suggested for prophylaxis in children (see also Uses and Administration, above).

Dietary measures, such as addition of vitamin-C-rich foods, or other enhancers of iron absorption including iron in the form of haem (found in meat or fish) to the diet, control of parasitic infections such as hookworm (which are responsible for considerable occult blood loss), and malaria prophylaxis are particularly important for the general community in developing countries. Fortification of food staples poses technical problems as iron salts react with food components and may produce rancidity or other undesirable changes on storage. Nonetheless, wheat or maize flour, rice, and milk products have been fortified in some countries, and consideration has also been given to fortification of salt or sugar.

1. Provan D. Iron deficiency anaemia. In: Provan D, ed. *ABC of clinical haematology.* 2nd ed. London: BMJ Books, 2003: 1–4.
2. World Health Organization. *Iron deficiency anaemia assessment, prevention, and control: a guide for programme managers.* Geneva: WHO, 2001. Available at: http://www.who.int/entity/nutrition/publications/en/ida_assessment_prevention_control.pdf (accessed 11/07/06)
3. British Society of Gastroenterology. Guidelines for the management of iron deficiency anaemia (issued May 2005). Available at: http://www.bsg.org.uk/pdf_word_docs/iron_def.pdf (accessed 09/11/05)
4. Zimmermann MB, Hurrell RF. Nutritional iron deficiency. *Lancet* 2007; **370:** 511–20.
5. National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease in adults. *Am J Kidney Dis* 2006; **47** (suppl 3): S16–S85. Correction. *ibid.*; **48:** 518. Also available at: http://www.kidney.org/professionals/KDOQI/guidelines_anemia/index.htm (accessed 04/12/06)
6. US Preventive Services Task Force. Routine iron supplementation during pregnancy: review article. *JAMA* 1993; **270:** 2848–54.
7. US Preventive Services Task Force. Routine iron supplementation during pregnancy: policy statement. *JAMA* 1993; **270:** 2846–8.

Restless legs syndrome. Iron deficiency is present in about a quarter of people with restless legs syndrome (see Sleep-associated Movement Disorders, p.958), particularly older people, and serum ferritin concentrations are inversely correlated with the severity of symptoms. Iron may have a role in the pathophysiology of the disorder, and treatment of iron deficiency may reduce symptoms.[1]

1. Medcalf P, Bhatia KP. Restless legs syndrome. *BMJ* 2006; **333:** 457–8.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Celloids IP 82; ***Austria:*** Liquifer†; ***Braz.:*** Ferrini; ***Indon.:*** Ferromia; ***Ital.:*** Liquifer†; Profer; ***Jpn:*** Ferromia; ***Malaysia:*** Ferrocyte; ***Mex.:*** Unifer; ***Singapore:*** Ferrocyte; ***Thai.:*** Ferrocyte; ***USA:*** EZFE; Icar; Ircon.

Multi-ingredient: ***Arg.:*** Hierroquick; ***Austral.:*** Celloid Compounds Magcal Plus; Celloid Compounds Sodical Plus; Clements Iron; Duo Celloids CPIP; Duo Celloids PCIP; Duo Celloids PPIP; Duo Celloids SPIP; Iron Compound†; ***Austria:*** China-Eisenwein; ***Braz.:*** Fernni Folico; Ferrumvit†; Folifer; Hemofer†; Olohepat†; Sadol; Sangotone†; Vi-Ferrin; ***Cz.:*** Homeovox; ***Ger.:*** Biovital Classic; Ferrodix†; Folicombin; ***Hung.:*** Biovital†; ***India:*** Cafe-Kit†; Carboflot†; Cofol Z; Fexid-Z; Imax; Probofex; Tonoferon; ***Indon.:*** Ferlin; Ferofort; Incremin with Iron; ***Ital.:*** Carfosid; Evafer; ***Mex.:*** Ferricol; Forta; Intrafer; Intrafer F-800; Intrafer TF; Uniferfol; ***NZ:*** Incremin with Iron; ***Philipp.:*** Incremin; Odiron; Odiron-C; ***Singapore:*** Memolobat†; ***Switz.:*** Elixir tonique N; ***Thai.:*** Hemo-Cyto-Serum; ***Turk.:*** Blood Builder; ***UK:*** Hematinic; ***USA:*** Centurion A–Z†; Feocyte; FeoGen; Geritol Complete; I-L-X; Icar-C Plus; Ircon-FA†; Renatabs with Iron; Tandem F; Theravee Hematinic; Ultra-Natal.

Iron Dextran

Demir Dekstran; Hierro dextrano; Iron-Dextran Complex.
CAS — 9004-66-4.
ATC Vet — QB03AB90; QB03AC90.

Pharmacopoeias. *Br.*, *Chin.*, and *US* include injections.
BP 2008 (Iron Dextran Injection). A sterile colloidal solution containing a complex of ferric hydroxide and dextrans of weight average molecular weight between 5000 and 7000. It contains 4.75 to 5.25% of iron and 17.0 to 23.0% of dextrans. pH 5.2 to 6.5.
USP 31 (Iron Dextran Injection). A sterile colloidal solution of ferric hydroxide in complex with partially hydrolysed dextran of low molecular weight. It may contain not more than 0.5% of phenol as a preservative. pH 5.2 to 6.5.

Adverse Effects and Treatment

Severe anaphylactoid reactions may occur with iron dextran and fatalities have been reported. It is therefore recommended that it be given where there are facilities for the emergency treatment of such reactions, that certain precautions be observed, and that test doses be used (see Precautions, below).

Rapid intravenous use may be associated with vascular flushing and hypotension. Thrombophlebitis may occur at the site of injection, although the incidence can be reduced by giving iron dextran in sodium chloride 0.9% rather than glucose 5%. Intramuscular injection is associated with local reactions, pain, and staining at the site of injection; leakage along the injection track may occur unless the proper technique is used (see Uses and Administration, below). Cardiovascular effects such as chest pain or tightness, shock, myocardial infarction, hypertension, tachycardia, bradycardia, and arrhythmias may occur with either route. Rashes, urticaria, purpura, and pruritus have been reported. Other reactions include gastrointestinal disturbances, haematuria, dyspnoea, and taste disturbance.

Patients may also experience delayed reactions 1 to 2 days after injection of iron dextran, such as backache, arthralgia, myalgia, lymphadenopathy, chills, fever, paraesthesia, dizziness, malaise, headache, nausea, and vomiting.

Overdose of parenteral iron is unlikely to be associated with any acute manifestations. Unwarranted parenteral iron therapy will result in iron overload and excess storage of iron (haemochromatosis) in the long term. The consequences of this include liver and endocrine dysfunction and heart disease (see Iron Overload, p.1949), and possibly an increased risk of infection (see Infections, under Precautions for Iron, p.1950). Iron overload may require chelation therapy with desferrioxamine (p.1441).

Intramuscular injection of iron complexes such as iron dextran has resulted in sarcomas at the injection site in *animals*. There is some evidence that this may occur in humans.

Effects on the blood. A 1-year-old girl with Down's syndrome and iron-deficiency anaemia was given three intramuscular injections of iron dextran over 6 days (to a total of 30 mg/kg). Pancytopenia developed subsequently, which reappeared when challenged with iron dextran. Tests indicated an allergic pathogenesis for the pancytopenia.[1] For further discussion of hypersensitivity reactions to iron dextran, see under Hypersensitivity, below.

Thrombocytopenia has also been reported after iron dextran[2] and iron sucrose[3] therapy.

1. Hurvitz H, *et al.* Pancytopenia caused by iron-dextran. *Arch Dis Child* 1986; **61:** 194–6.
2. Go RS, *et al.* Thrombocytopenia after iron dextran administration in a patient with severe iron deficiency anemia. *Ann Intern Med* 2000; **132:** 925.
3. Taskapan H, *et al.* Transient severe thrombocytopenia in a patient on CAPD after intravenous iron administration. *Perit Dial Int* 2003; **23:** 408–9.

Hypersensitivity. The Boston Collaborative Drug Surveillance Program monitored consecutively 32 812 medical inpatients. Drug-induced anaphylaxis occurred in 1 of 169 patients given iron dextran (route not stated).[1] An investigation of 481 persons given a total of 2099 intravenous injections of iron dextran found 3 life-threatening immediate anaphylactoid reactions; 8 severe delayed reactions were also observed, and many reactions of a less serious nature.[2] In a more recent series,[3] 10 of 573 patients had anaphylactoid reactions after intravenous iron dextran. Other serious reactions included 1 case of cardiac arrest, and 3 cases of dyspnoea, hypertension, or chest pain.

Test doses are recommended before giving a full therapeutic dose (see Uses and Administration, below) and emergency measures for the treatment of allergic reactions should be available. A desensitisation protocol has been used successfully in a patient who reacted to the test dose[4] and in a patient with a previous life-threatening reaction to iron infusion;[5] methylprednisolone 50 mg was given intravenously at 13 hours, 7 hours, and 1 hour before iron dextran, and diphenhydramine 50 mg and ephedrine 25 mg were given intramuscularly 1 hour before infusion. Dextran 1 (p.1058) was given just before the iron dextran infusion. Approximately 2 g of iron was then given over a period of about 4 days.

It is not clear whether hypersensitivity to iron dextran is due to the dextran or the iron component.[6-8] When compared with lower molecular-weight iron dextran, a higher molecular-weight iron dextran was reported to be associated with significantly higher rates of adverse reactions,[7,9,10] including fatalities and anaphylactoid reactions;[9] some have called for the use of high-molecular-weight iron dextran to be abandoned.[11] Reviews[6,8,12] suggest that parenteral dextran-free iron compounds such as iron sucrose or sodium ferric gluconate complex may be safer alternatives to iron dextran. Iron sucrose has been reported to be well tolerated in patients previously intolerant to iron dextran, sodium ferric gluconate complex, or both.[13] However, adverse reactions have still been reported in patients treated with dextran-free preparations,[8,14] and some have challenged the view that they are safer than iron dextran.[15,16]

In a report of a lupus-like disorder associated with use of iron dextran,[17] the illness resolved with appropriate treatment but recurred on rechallenge.

For discussion of pancytopenia believed to have an underlying allergic pathogenesis, see Effects on the Blood, above.

1. Porter J, Jick H. Drug-induced anaphylaxis, convulsions, deafness, and extrapyramidal symptoms. *Lancet* 1977; **i:** 587–8.
2. Hamstra RD, *et al.* Intravenous iron dextran in clinical medicine. *JAMA* 1980; **243:** 1726–31.
3. Fishbane S, *et al.* The safety of intravenous iron dextran in hemodialysis patients. *Am J Kidney Dis* 1996; **28:** 529–34.
4. Monaghan MS, *et al.* Safe administration of iron dextran to a patient who reacted to the test dose. *South Med J* 1994; **87:** 1010–12.
5. Hickman MA, *et al.* Successful administration of iron dextran in a patient who experienced a life threatening reaction to intravenous iron dextran. *Ann Allergy Asthma Immunol* 2000; **84:** 262–3.
6. Fishbane S. Safety in iron management. *Am J Kidney Dis* 2003; **141** (suppl): S18–S26.
7. McCarthy JT, *et al.* Adverse events in chronic hemodialysis patients receiving intravenous iron dextran—a comparison of two products. *Am J Nephrol* 2000; **20:** 455–62.
8. Fishbane S, Kowalski EA. The comparative safety of intravenous iron dextran, iron saccharate, and sodium ferric gluconate. *Semin Dial* 2000; **13:** 381–4.
9. Chertow GM, *et al.* On the relative safety of parenteral iron formulations. *Nephrol Dial Transplant* 2004; **19:** 1571–5.
10. Auerbach M, *et al.* Clinical update: intravenous iron for anaemia. *Lancet* 2007; **369:** 1502–4.
11. Auerbach M, Rodgers GM. Intravenous iron. *N Engl J Med* 2007; **357:** 93–4.
12. Silverstein SB, Rodgers GM. Parenteral iron therapy options. *Am J Hematol* 2004; **76:** 74–8.
13. Charytan C, *et al.* Safety of iron sucrose in hemodialysis patients intolerant to other parenteral iron products. *Nephron Clin Pract* 2004; **96:** c63–c66.
14. Saadeh CE, Srkalovic G. Acute hypersensitivity reaction to ferric gluconate in a premedicated patient. *Ann Pharmacother* 2005; **39:** 2124–7.
15. Eichbaum Q, *et al.* Is iron gluconate really safer than iron dextran? *Blood* 2003; **101:** 3756–7.
16. Auerbach M, Al Talib K. Low-molecular weight iron dextran and iron sucrose have similar comparative safety profiles in chronic kidney disease. *Kidney Int* 2008; **73:** 528–30.
17. Oh VMS. Iron dextran and systemic lupus erythematosus. *BMJ* 1992; **305:** 1000.

Overdosage. A 29-year-old woman was given 32 mL iron dextran (*Imferon*) intravenously. Twenty-four hours later she developed muscle cramps, bilateral frontal headaches, with subsequent neck stiffness, and marked opisthotonia with photophobia.[1] The haemoglobin concentration did not rise after the infusion of iron which indicated there had been no iron deficiency. Thus, abnormally high concentrations of free iron had followed the iron therapy and this free iron was able to cross into the CSF and was responsible for the meningitic symptoms.

1. Shuttleworth D, *et al.* Meningism due to intravenous iron dextran. *Lancet* 1983; **ii:** 453.

Precautions

Iron dextran is contra-indicated in patients with severe liver damage or acute kidney infection. It is also contra-indicated in persons with a history of hypersensitivity to the preparation. Teratogenicity has been demonstrated in non-anaemic *animals* given the equivalent of about three times the maximum human dose and its use should be avoided in pregnancy if possible.

Additionally, iron dextran should be given with caution to patients with a history of allergic disorders or asthma and in these patients the intramuscular, and not the intravenous, route should be used. Patients with rheumatoid arthritis may develop worsening of symptoms when given iron dextran intravenously. Patients with other inflammatory disorders may be at increased risk of delayed reactions. Large doses of iron dextran by infusion may lead to serum discoloration; this should not be mistaken as evidence of haemolysis. Oral iron salts should be stopped before giving parenteral iron.

A test dose should be given before a full therapeutic dose is given (see Uses and Administration, below) and emergency measures for the treatment of allergic reactions should be available (see Anaphylaxis and Anaphylactic Shock, p.1205). Patients should be kept under observation for at least 1 hour after a test dose or after intravenous doses.

Iron dextran formulated with phenol as a preservative is intended to be given by the intramuscular route only.

Interactions

As for Iron, p.1950.

Enalapril. Enalapril may possibly potentiate the adverse systemic reactions seen with intravenous iron therapy.[1]

1. Rolla G, *et al.* Systemic reactions to intravenous iron therapy in patients receiving angiotensin-converting enzyme inhibitor. *J Allergy Clin Immunol* 1994; **93:** 1074–5.

Pharmacokinetics

After intramuscular injection iron dextran is absorbed primarily through the lymphatic system: most is absorbed after 3 days and the remainder over 3 to 4 weeks. A variable portion may become fixed in the muscle for several weeks or months. After intravenous infusion, iron dextran is taken up by the cells of the reticuloendothelial cells, particularly in the liver and spleen. The reticuloendothelial cells gradually separate iron from the iron-dextran complex; the distribution and elimination of iron is described on p.1950.

Uses and Administration

Iron dextran is given by injection, and should be used only in the treatment of proven iron-deficiency anaemia (p.1951) where oral therapy is ineffective or impracticable.

For iron-deficiency anaemia, total dosage is **calculated** according to the haemoglobin concentration and body-weight of the patient; allowance is also made for additional iron to replenish iron stores. Iron dextran injection is usually supplied with a table from which the recommended dose can be obtained for patients of different weights and haemoglobin (Hb) status. There may be variations between countries in the doses obtained from such tables. Doses can also be calculated from various formulae. A typical formula used for a preparation containing the equivalent of 50 mg/mL of iron is:

$$\text{Dose in mL} = \{0.0442 \times \text{body-weight (kg)} \times [\text{desired Hb level (g/100 mL)} - \text{measured Hb level}]\} + (0.26 \times \text{body-weight})$$

In adults, the calculated lean body-weight should normally be used in this formula rather than the actual body-weight. Note that doses obtained from tables or the above formulae are for iron-deficiency anaemia, and are not suitable for iron replacement for simple blood loss.

Before starting therapy, all patients should receive a **test** dose via the intended route, and should be observed for adverse reactions (see Precautions, above).

The total dose requirement may be given as a series of **intramuscular** injections daily or once or twice weekly. It is given by deep intramuscular injection into the upper outer quadrant of the buttock; to prevent leakage along the injection track, the subcutaneous tissue is drawn to one side before the needle is inserted. Before the first therapeutic dose, a test dose should be given and the patient observed for at least 1 hour: a dose of 0.2 mL (10 mg) has been suggested for children weighing less than 10 kg, 0.3 mL (15 mg) for those weighing 10 to 20 kg, and 0.5 mL (25 mg) for adults. A suggested daily maximum dosage for children is: less than 5 kg, up to 0.5 mL (25 mg); 5 to 9 kg, up to 1 mL (50 mg). Larger children and adults normally receive 2 mL (100 mg).

Iron dextran is also given **intravenously** either by total-dose infusion (TDI) or as divided injections. A test dose of 25 mg is given before the first therapeutic dose and the patient is observed for at least 1 hour; if no adverse reactions occur within that time, the remainder of the initial dose may be given. For subsequent doses, the first portion of the dose is given more slowly than the remainder of the dose, during which time the patient is observed for adverse reactions; recommendations for the rate at which this is done may vary in different countries.

In total-dose infusion, the total dose calculated according to the haemoglobin concentration (as outlined above) is given by slow intravenous infusion in about 500 mL of sodium chloride 0.9% or glucose 5%; sodium chloride may be preferable because of the reduced incidence of thrombophlebitis. The first 25 mg of iron should be infused over 15 minutes, and if no adverse reaction has occurred during this time the rate of infusion may be increased progressively to 45 to 60 drops/minute; the infusion usually takes 4 to 6 hours.

For divided intravenous use, the total dose is also calculated according to the haemoglobin concentration. In the UK, the usual recommended dosage schedule is 100 to 200 mg of iron given 2 to 3 times weekly until the total dose has been given. It may be given diluted in 10 to 20 mL of sodium chloride 0.9% or glucose 5%; the first 25 mg of iron is given slowly over 1 to 2 minutes. If no adverse reactions occur within 15 minutes, the remaining portion of the dose is given. Alternatively, 100 to 200 mg may be diluted in 100 mL of

sodium chloride 0.9% or glucose 5%; the first 25 mg of iron is given over 15 minutes and if no adverse reactions occur during this time, the remaining portion of the infusion is given at a rate of not more than 100 mL in 30 minutes. In the USA, the injection may be given undiluted at a rate not exceeding 50 mg iron (1 mL) per minute; maximum daily doses are similar to those given for intramuscular injection.

Preparations

BP 2008: Iron Dextran Injection;
USP 31: Iron Dextran Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Fexiron; ***Belg.:*** Fercayl; ***Canad.:*** Dexiron; Infufer; ***Denm.:*** Cosmofer; ***Ger.:*** Cosmofer; ***Gr.:*** Cosmofer; ***Hong Kong:*** Cosmofer†; ***India:*** Imferon; ***Indon.:*** Hibiron; ***Irl.:*** Cosmofer; ***Mex.:*** Driken; Ferrocel; Ferroin†; Hidex; Irondex; ***Norw.:*** Cosmofer; ***Philipp.:*** Cosmofer; ***Port.:*** Cosmofer; ***Spain:*** Imferon†; ***Switz.:*** Ferrum Hausmann; ***Thai.:*** Cosmofer; ***Turk.:*** Cosmofer; ***UK:*** Cosmofer; ***USA:*** DexFerrum; INFeD; ***Venez.:*** Cosmofer.

Iron Polymaltose

Demir III Hidroksit Polimaltoz; Ferromaltose; Ferrum Polyisomaltose; Hierro polimaltosa.

Profile

Iron polymaltose is a complex of ferric hydroxide and isomaltose. It is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is given orally in usual doses containing the equivalent of 100 mg of iron daily although up to 300 mg daily has been given in some countries. It is also given parenterally, the total dose being calculated and given by intravenous infusion or, preferably, as a series of intramuscular injections containing the equivalent of up to 200 mg of iron in a single day; injections are usually given only every few days. For further information relating to the parenteral use of iron, see Iron Dextran, p.1951.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ferranin; Maltofer; Siderblut; Vitalix; ***Austral.:*** Ferrosig; Ferrum H; ***Austria:*** Ferrum Hausmann; ***Braz.:*** Noripurum; Ultrafer; ***Chile:*** Ferium; Maltofer; ***Cz.:*** Ferrum; Maltofer; ***Fin.:*** Maltofer; ***Fr.:*** Maltofer†; ***Ger.:*** Ferrum Hausmann; ***Gr.:*** Antianem; Dextrifer; Ferrobest; Ferrum Hausmann; Hemafer; Hydrofer-3; Veltifer; ***Hong Kong:*** Ferrum Hausmann; ***Hung.:*** Maltofer; ***India:*** Fericip; Mumfer; Phosfomin Iron; ***Indon.:*** Maltofer; ***Irl.:*** Ferrum; ***Israel:*** Ferripel; ***Ital.:*** Intrafer; ***Malaysia:*** Maltofer; Saferon; ***Mex.:*** Ferranina; ***NZ:*** Ferrosig; Ferrum H; ***Pol.:*** Ferrum Lek; ***Port.:*** Ferrum Hausmann; Maltofer; ***Rus.:*** Ferrum Lek (Феррум Лек); ***S.Afr.:*** Ferrimed; Ferrimed DS; ***Singapore:*** Ferrum Hausmann; ***Switz.:*** Maltofer; ***Turk.:*** Ferrum Hausmann; Maltofer; ***Venez.:*** Intafer; Maltofer.

Multi-ingredient: ***Arg.:*** Ferranin Complex; Hierro Dupofol; Isis Fe; Maltofer Fol†; Siderblut Folic; Tenvic; Vitalix Complex; ***Braz.:*** Noripurum Folico; Noripurum Vitaminado; ***Chile:*** Maltofer Fol; ***Cz.:*** Maltofer Fol; ***Gr.:*** Dextrifer-Fol; Ferrum Fol Hausmann; Hemafer fol; ***Hong Kong:*** Eurofer; ***Hung.:*** Maltofer Fol; ***India:*** Fericip; Hepofer; Mumfer-Z†; Mumfer†; ***Indon.:*** Feritrin; Maltofer Fol; ***Israel:*** Ferrifol; ***Malaysia:*** Maltofer; ***Mex.:*** Ferranina Complex; Ferranina Fol; Ironfol; ***Philipp.:*** Eurofer; ***Port.:*** Ferrum Fol; Maltoferfol; ***S.Afr.:*** Ferrimed; ***Singapore:*** Eurofer; Saferon†; ***Switz.:*** Maltofer Fol; ***Thai.:*** Eurofer; Orofer; ***Turk.:*** Ferrum Fort Hausmann; Maltofer Fol; ***Venez.:*** Intafer; Intaferfol; Maltoferfol.

Iron Sorbitol

Astra-1572; Demir Sorbitol; Hierro sorbitol; Iron Sorbitex *(USAN)*; Iron-Sorbitol-Citric Acid Complex.

CAS — 1338-16-5.
ATC Vet — QB03AC03.

Pharmacopoeias. *US* includes an injection.
USP 31 (Iron Sorbitex Injection). A sterile solution of a complex of iron, sorbitol, and citric acid that is stabilised with the aid of dextrin and an excess of sorbitol. pH 7.2 to 7.9.

Adverse Effects, Treatment, and Precautions

As for Iron Dextran, p.1951.

There may be severe systemic reactions; cardiac complications, such as complete AV block, ventricular tachycardia, and atrial or ventricular fibrillation, may be fatal. The urine of patients treated with iron sorbitol may become dark on standing.

Iron sorbitol should not be given intravenously. It should preferably be avoided in patients with pre-existing cardiac abnormalities.

Effects on the heart. A description of adverse events in 3 patients with the malabsorption syndrome treated with intramuscular injections of iron sorbitol.[1] Two patients died; in one, findings were consistent with anaphylaxis but in the other cardiac toxicity was considered to be due to a direct effect. In the third patient direct cardiac toxicity was also implicated. In another report,[2] a patient developed cardiac arrhythmia after his seventh injection of iron sorbitol. He was found to have a low serum concentration of alpha-tocopherol, supposed by the authors to be caused by the patient's malabsorption syndrome. This had apparently predisposed the patient to arrhythmia by contributing to myocardial cell sensitivity to lipid peroxidation, which is catalysed by ferrous ions. Insufficient alpha-tocopherol to scavenge the free radicals generated by the iron could also have led to loss of myocardial fatty acids, thereby disturbing membrane function. It was suggested that iron sorbitol was a less stable form of iron than iron dextran, and should be given with extreme caution to patients with malabsorption and low levels of alpha-tocopherol.

1. Karhunen P, *et al*. Reaction to iron sorbitol injection in three cases of malabsorption. *BMJ* 1970; **2:** 521–2.
2. Lindvall S, *et al*. Alpha-tocopherol and cardiac toxicity of iron. *Scand J Haematol* 1980; **25:** 331–8.

Interactions

As for Iron Dextran, p.1952.

Pharmacokinetics

About 66% of iron sorbitol is absorbed within 3 hours of intramuscular injection, most of it directly into the blood circulation, and some via the lymphatic system. Almost all is absorbed within about 10 days. Clearance of iron sorbitol from the plasma is rapid, and is mainly via the reticuloendothelial system, as described for Iron Dextran, p.1952.

Uses and Administration

Iron sorbitol should be used only in the treatment of proven iron-deficiency anaemia (p.1951) where oral therapy is ineffective or impracticable.

It is given by deep intramuscular injection into the upper outer quadrant of the buttock; to prevent leakage along the injection track, the subcutaneous tissue is drawn to one side before the needle is inserted.

Total dosage is calculated according to body-weight and the haemoglobin concentration of the blood, and tables are usually provided with iron sorbitol injections for this purpose. The recommended single dose is the equivalent of 1.5 mg/kg of iron up to a maximum of 100 mg daily; these doses are then given daily or every other day until the required haemoglobin concentration has been achieved. Iron sorbitol is not recommended in children weighing under 3 kg.

Iron sorbitol should not be given intravenously.

Preparations

USP 31: Iron Sorbitex Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Yectafer; ***Canad.:*** Jectofer†; ***Ger.:*** Jectofer†; ***India:*** Jectocos; ***Irl.:*** Jectofer†; ***Norw.:*** Jectofer†; ***Turk.:*** Jectofer.

Multi-ingredient: ***Arg.:*** Yectafer Complex; ***India:*** Jectocos Plus.

Iron Succinyl-Protein Complex

Demir III Protein Süksinat; Ferro Proteinsuccinilato; Hierro succinil-proteína, complejo de; Iron Proteinsuccinylate; ITF-282; Proteinsuccilinato de hierro.

CAS — 93615-44-2.
ATC — B03AB09.
ATC Vet — QB03AB09.

Profile

Iron succinyl-protein complex is a source of iron (p.1949) used for iron-deficiency anaemia (p.1951). It is given orally in doses of up to 1.6 g daily (equivalent to up to 80 mg of iron daily).

◊ References.

1. Köpcke W, Sauerland MC. Meta-analysis of efficacy and tolerability data on iron proteinsuccinylate in patients with iron deficiency anemia of different severity. *Arzneimittelforschung* 1995; **45:** 1211–16.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ferplex; ***Braz.:*** Fisiofer†; ***Chile:*** Fisiofer; Legofer; ***Cz.:*** Ferplex; ***Gr.:*** Fysiofer; Legofer; ***Ital.:*** Ferlatum; Ferplex; Ferremon†; Folinemic Ferro†; Legofer†; Pemexin; Proteoferrina; Rekord Ferro; ***Mex.:*** Ferxal; ***Pol.:*** Ferplex; ***Port.:*** Fervit; Fetrival; Legofer; ***Rus.:*** Ferlatum (Ферлатум); ***Spain:*** Ferplex; Ferrocur; Lactoferrina; ***Turk.:*** Ferplex.

Multi-ingredient: ***Gr.:*** Fysiofol; ***Ital.:*** Ferrofolin; ***Turk.:*** Ferplex Fol.

Iron Sucrose *(BAN, USAN)*

Demir Sükroz; Eisenzucker; Ferri oxidum saccharatum; Ferric Hydroxide Sucrose; Ferric Oxide, Saccharated; Ferrique (oxyde) sucré; Ferrum Oxydatum Saccharatum; Hierro sacarosa; Iron (III) hydroxide-sucrose complex; Iron Saccharate; Oxyde de Fer Sucré; Saccharated ferric oxide; Saccharated Iron Oxide; XI-921.

CAS — 8047-67-4.
ATC — B03AB02; B03AC02.
ATC Vet — QB03AB02; QB03AC02.

Pharmacopoeias. In *Swiss*.
US includes an injection.
USP 31 (Iron Sucrose Injection). A sterile, colloidal solution of ferric hydroxide in complex with sucrose in water for injection. Sodium hydroxide may be added to adjust the pH. It contains no antimicrobial agent, chelating agent, dextran, gluconate, or other added substances. pH 10.5 to 11.1 at 20°. It is intended for intravenous use only. When given by intravenous infusion, it should be diluted with 0.9% sodium chloride injection to a concentration of 0.5 to 2.0 mg of elemental iron/mL. Do not allow to freeze.

Adverse Effects, Treatment, and Precautions

For parenteral iron, see Iron Dextran, p.1951. Iron sucrose injection is strongly alkaline and must not be given subcutaneously or intramuscularly. UK (but not US) licensed drug information contra-indicates its use in patients with a history of asthma, eczema, anaphylaxis, or other allergic disorders.

Effects on the blood. For a report of thrombocytopenia associated with iron sucrose, see under Iron Dextran, p.1952.

Hypersensitivity. For a discussion of whether iron sucrose may be a safer alternative to iron dextran, see p.1952.

Pharmacokinetics

Iron sucrose is rapidly cleared from the plasma after intravenous injection with a terminal half-life of about 6 hours. A competitive exchange of iron takes place from the iron sucrose complex to the iron-binding protein transferrin. About 5% of a dose is eliminated via the kidneys in the first 4 hours after a dose.

Uses and Administration

Iron sucrose is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is given when oral iron therapy is ineffective or impractical, by slow intravenous injection, or intravenous infusion; when used in haemodialysis patients, it may be given into the venous limb of the dialyser. The dose is calculated according to body-weight and iron deficit. In the UK the cumulative dose is given in single doses of 100 mg of iron not more than three times weekly; if rapid delivery is required, the dose may be increased up to 200 mg not more than three times weekly. The dose may be given undiluted at a rate of 20 mg/minute, after a test dose of 20 mg of iron has been given over 1 to 2 minutes. Alternatively, 100 mg is diluted in a maximum of 100 mL of sodium chloride 0.9% and the first 25 mg given as a test dose over 15 minutes; the remaining portion is given at a rate not exceeding 50 mL per 15 minutes.

In the USA, a similar dose is given for haemodialysis patients receiving supplemental erythropoietin therapy, to a total cumulative dose of 1 g. For peritoneal dialysis patients on erythropoietin, two infusions of 300 mg over 1.5 hours are given 14 days apart, followed by an infusion of 400 mg over 2.5 hours 14 days later. The doses are diluted in a maximum of 250 mL of sodium chloride 0.9%. For patients not on dialysis, a total cumulative dose of 1 g is given over a 14-day period, as a 200 mg slow undiluted intravenous injection over 2 to 5 minutes on 5 separate occasions within this time. Iron sucrose has also been given orally.

Anaemia of chronic renal failure. References.

1. Charytan C, *et al*. Efficacy and safety of iron sucrose for iron deficiency in patients with dialysis-associated anemia: North American clinical trial. *Am J Kidney Dis* 2001; **37:** 300–7.
2. Stoves J, *et al*. A randomized study of oral vs intravenous iron supplementation in patients with progressive renal insufficiency treated with erythropoietin. *Nephrol Dial Transplant* 2001; **16:** 967–74.
3. Chandler G, *et al*. Intravenous iron sucrose: establishing a safe dose. *Am J Kidney Dis* 2001; **38:** 988–91.
4. Blaustein DA, *et al*. The safety and efficacy of an accelerated iron sucrose dosing regimen in patients with chronic kidney disease. *Kidney Int* 2003; (suppl): S72–S77.
5. Charytan C, *et al*. Safety of iron sucrose in hemodialysis patients intolerant to other parenteral iron products. *Nephron Clin Pract* 2004; **96:** 63–6.
6. Leijn E, *et al*. Intravenous iron supplementation in children on hemodialysis. *J Nephrol* 2004; **17:** 423–6.
7. Aronoff GR, *et al*. Iron sucrose in hemodialysis patients: safety of replacement and maintenance regimens. *Kidney Int* 2004; **66:** 1193–8.
8. Van Wyck DB, *et al*. The United States Iron Sucrose (Venofer) Clinical Trials Group. A randomized, controlled trial comparing IV iron sucrose to oral iron in anemic patients with nondialysis-dependent CKD. *Kidney Int* 2005; **68:** 2846–56.
9. Hollands JM, *et al*. Safety of high-dose iron sucrose infusion in hospitalized patients with chronic kidney disease. *Am J Health-Syst Pharm* 2006; **63:** 731–4.

Preparations

USP 31: Iron Sucrose Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Energavit; Ferricrine; Sucrox; Venofer; ***Austral.:*** Venofer; ***Belg.:*** Venofer; ***Canad.:*** Venofer; ***Chile:*** Rafofer; Venofer; ***Cz.:*** Ferrologic; Ferrum; Venofer; ***Denm.:*** Venofer; ***Fin.:*** Venofer; ***Fr.:*** Venofer; ***Ger.:*** FERROinfant Neu†; Venofer; ***Gr.:*** Anemifer; Felix; Ferroprol; Ferrovin; Venofer; ***Hong Kong:*** Venofer; ***Hung.:*** Venofer; ***Indon.:*** Venofer; ***Israel:*** Venofer; ***Ital.:***