1. PRODUCT NAME

Ferrosig, Solution for Injection, 50 mg/mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 mL ampoule of Ferrosig Solution for Injection contains 318 mg iron polymaltose equivalent to 100 mg iron III.

3. PHARMACEUTICAL FORM

A slightly viscous dark reddish brown liquid. Odour faintly malt-like. Each 2 mL ampoule of Ferrosig contains the equivalent of 100 mg of iron.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the prevention and treatment of iron deficiency anaemia when oral preparations are contraindicated or in the following circumstances:

- When enteric absorption of iron is defective
- When patient non-compliance or persistent gastrointestinal intolerance makes oral therapy impractical.

The diagnosis must be based on laboratory tests. Intravenous use is only recommended for use in hospitals when the intramuscular route is impractical or unacceptable and when tests show that the bone marrow has no stored iron.

4.2 Dose and method of administration

(A) METHOD OF ADMINISTRATION

Intramuscular Use

Technique of Injection: The technique of injection is of crucial importance. Iron polymaltose should never be injected into the arm or other exposed areas. The wrong injection technique may result in pain and persistent discolouration of the skin.

The following method of ventro-gluteal injection according to HOCHSTETTER is recommended instead of the normal method of injection in the top outer quadrant of the gluteus maximus muscle:

1. The length of the needle should be at least 5 - 6 cm. The lumen of the needle should not be too wide.

2. The site of injection is determined as follows (see Fig. 1): First point A is found, corresponding to the ventral iliac spine. If the patient lies on the right side, for instance, the middle finger of the left hand is placed on point A. The index finger is extended away from the middle finger, so that it comes to lie below the iliac crest, at point B. The triangle lying between the proximal phalanges of the middle and index fingers represents the site of injection. This is disinfected in the usual way (Fig. 2).

3. Before the needle is inserted, the skin over the site of injection is pulled down, about 2 cm (Fig. 3), to give an S-shaped puncture channel. This prevents the injected solution from running back into the subcutaneous tissues and discolouring the skin.

4. The needle is introduced more or less vertically to the skin surface, angled to point towards the iliac crest rather than the hip joint (Fig. 4).

5. After the injection, the needle is slowly withdrawn and pressure from a finger applied beside the puncture site. This pressure is maintained for about one minute.

6. The patient should move about after the injection.

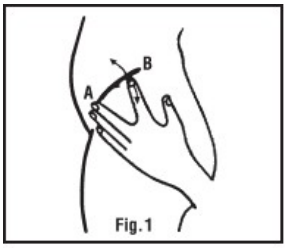

Fig.1

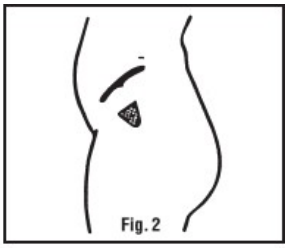
Fig.2

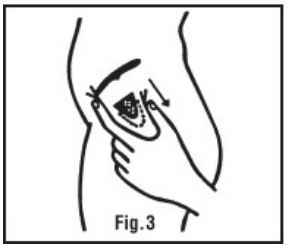
Fig.3

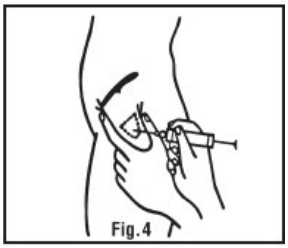
Fig.4

Intravenous Use

Total dose infusion of iron polymaltose complex is recommended only when the intramuscular route is impractical or unacceptable and when bone marrow shows no stored iron. It is suitable for use in hospitals only.

The total dose to be administered, calculated from the dosage table, is aseptically added to 500 mL of sterile, normal saline (up to 2500 mg may be given in 500 ml).

Notes

- Do not inject the iron into the tube of the administration set.
- The first 50 mL should be infused slowly (5 - 10 drops/minute (0.34 – 0.67 mL/minute)) and the patient observed carefully. If this is well tolerated, the rate may be increased to 30 drops/minute (2.01 mL/minute) - (based on a drop volume of 0.067 ml).
- The approximate total infusion time is 5 hours.
- Stop infusion immediately if any adverse reaction is noted.
- To avoid nausea and epigastric troubles the infusion rate should not be excessive.
- The infusion should not be mixed with any other therapeutic agents. If mixed with acidic substances or other substances with a strong reducing effect toxic iron compounds may be liberated from the compound.

(B) DOSING FOR INTRAMUSCULAR OR INTRAVENOUS USE

Calculation of Required Dose

The figures in the accompanying dosage table have been calculated using the following formula taken from GANZONI (Schweiz. Med. Wschr. 100, 301 - 303, 1970):

Iron dose (mg) = Hb-iron deficiency + iron depot

Hb-iron deficiency = body weight (kg) x (target Hb – actual Hb in g/L) x 0.24*
* factor 0.24 = 0.0034 x 0.07 x 1000

(For the purposes of this calculation, iron content of the haemoglobin = 0.34%, blood volume = 7% of the body weight, 1000 is the conversion from grams to milligrams).

Note: The above formula can also be used to calculate the total iron deficit.

Up to 34 kg body weight: target Hb = 130 g/L, iron depot = 15 mg/kg body weight (for a patient weighing 34 kg the iron depot is 34 x 15 = 500 mg).

Over 34 kg body weight: target Hb = 150 g/L, iron depot = 500 mg.

Example of Calculation

Assuming patient weighing 60 kg, target Hb 150 g/L, actual Hb 60 g/L then:
Iron dose (mg) = 60 x (150-60) x 0.24 + 500 mg = 1296 mg + 500 mg = 1800 mg iron
Therefore patient requires 1800 mg iron or 18 ampoules.

Dosage Table

Dosage table for the determination of the total millilitres of Ferrosig injection required.

Body Weight (kg)	Hb 60 g/L		Hb 75 g/L		Hb 90 g/L		Hb 105 g/L	
	mL	amp.	mL	amp.	mL	amp.	mL	amp.
5	3	1.5	3	1.5	3	1.5	2	1
10	6	3	6	3	5	2.5	4	2
15	10	5	9	4.5	7	3.5	6	3
20	13	6.5	11	5.5	10	5	8	4
25	16	8	14	7	12	6	11	5.5
30	19	9.5	17	8.5	15	7.5	13	6.5
35	25	12.5	23	11.5	20	10	18	9
40	27	13.5	24	12	22	11	19	9.5
45	30	15	26	13	23	11.5	20	10
50	32	16	28	14	24	12	21	10.5
55	34	17	30	15	26	13	22	11
60	36	18	32	16	27	13.5	23	11.5
65	38	19	33	16.5	29	14.5	24	12
70	40	20	35	17.5	30	15	25	12.5
75	42	21	37	18.5	32	16	26	13
80	45	22.5	39	19.5	33	16.5	27	13.5
85	47	23.5	41	20.5	34	17	28	14
90	49	24.5	43	21.5	36	18	29	14.5

Administer 2 mL by intramuscular injection every second day until the total dose is attained or administer 4 mL at longer intervals. Regular determination of Hb level is recommended.

Maximum Single Daily Dose by Intramuscular Injection

Infants up to 5 kg body weight:	0.5 mL
Children of 5 - 10 kg body weight:	1 mL
Patients weighing > 10 kg to 45 kg:	2 mL
Adults:	4 mL

4.3 Contraindications

Ferrosig should not be given to patients presenting with any of the following conditions:

- Hypersensitivity to iron(III) hydroxide polymaltose complex
- Anaemia not caused by simple iron deficiency (e.g. haemolytic anaemia, megablastic anaemia caused by Vitamin B12 deficiency, disturbances in erythropoesis, hypoplasia of the marrow)
- Iron overload (e.g. haemochromatosis, haemosiderosis)
- Ostler-Rendu-Weber syndrome
- Chronic polyarthritis
- Bronchial asthma
- Infectious renal complaints in acute phase
- Uncontrolled hyperparathyroidism
- Decompensated hepatic cirrhosis
- Infectious hepatitis
- During the first trimester of pregnancy

As elemental iron tends to accumulate in inflamed tissues, parenteral iron should not be given to patients with severe inflammation or infection of the kidney or liver.

4.4 Special warnings and precautions for use

Since parenteral use of complexes of iron and carbohydrates has resulted in fatal anaphylactoid reactions, iron polymaltose should be used only in patients in whom a clearly established indication for parenteral iron therapy exists, confirmed by appropriate laboratory tests. In the case of a mild allergic reaction, antihistamines should be administered immediately.

Anaphylactoid reactions occur most frequently within the first several minutes of administration and are generally characterised by sudden onset of respiratory difficulties, tachycardia and hypotension. Ferrosig should only be administered when personnel trained to evaluate and manage anaphylactic reactions, and resuscitative interventions, are immediately available. Each patient should be monitored for signs and symptoms of hypersensitivity during and after each administration of intravenous iron for at least 30 minutes. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately.

There have been reports that hypersensitivity reactions may include Kounis syndrome (acute coronary arteriospasm).

Patients with bronchial asthma, with low iron binding capacity and/or folic acid deficiency are particularly at risk of an allergic or anaphylactoid reaction. Caution is also recommended in patients with allergies, hepatic and renal insufficiency or cardiovascular disease.

Patients with rheumatoid arthritis and possibly other inflammatory diseases (e.g. ankylosing spondylitis, lupus erythematosus) may be at particular risk of delayed reactions, including fever and exacerbation or reactivation of joint pain.

Iron may increase the pathogenicity of certain micro-organisms. The use of intramuscular iron in neonates has been associated with an increased incidence of Gram negative sepsis, principally infections caused by *E. coli*.

Unwarranted administration of parenteral iron preparations may cause excess storage of iron and a syndrome similar to haemosiderosis in patients whose anaemia is not attributable to iron deficiency eg. those with haemoglobulinopathies.

4.5 Interaction with other medicines and other forms of interaction

As with all parenteral iron preparations, Ferrosig should not be administered concomitantly with oral iron preparations as the absorption of oral iron is reduced. Oral iron therapy should not commence until at least one week after the last iron injection.

Concomitant administration of ACE inhibitors can increase the incidence of adverse effects associated with parenteral iron preparations (eg Erythema, abdominal cramps, nausea, vomiting and hypotension).

4.6 Fertility, pregnancy and lactation

Ferrosig should not be administered in the first trimester of pregnancy. Ferrosig should only be administered in the second and third trimester of pregnancy if the benefits of treatment outweigh the potential risk to the foetus. No controlled studies are available on animal or on pregnant women.

There have been reports of foetal bradycardia occurring after administration to pregnant women. The foetal bradycardia was usually transient and associated with a hypersensitivity reaction in the mother.

4.7 Effects on ability to drive and use machines

Not stated.

4.8 Undesirable effects

Adverse reactions to parenteral Ferrosig have only been reported infrequently. However, the following reactions are known to have occurred after parenteral iron therapy:

General
- Flushing, sweating, chills and fever
- Chest and back pain

Injection site reactions
- Pain at injection site
- Local inflammation with inguinal lymphadenopathy
- Lower quadrant abdominal pain

Hypersensitivity
- Anaphylaxis

Gastrointestinal
- Nausea and vomiting

Central nervous System
- Headache
- Dizziness

Musculoskeletal
- Joint and muscle pain
- Arthralgia
- Sensation of stiffening of the arms, legs or face

Cardiovascular
- Fainting
- Syncope
- Tachycardia
- Hypotension
- Circulatory collapse

Respiratory
- Bronchospasm with dyspnoea

Haematological
- Generalised lymphadenopathy

Dermatological
- Rash
- Urticaria
- Angioneurotic oedema

Adverse reactions may be delayed by 1 - 2 days after treatment with Ferrosig injection.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Overdosage of iron causes haemosiderosis and consequent cirrhosis of the liver, diabetes and heart failure. Periodic monitoring of serum ferritin may be useful in recognising a deleterious, progressive accumulation of iron.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Actions

Ferrosig is an aqueous, approximately isotonic solution for intramuscular injection. The complex is stable over a wide pH range (1 - 14) and each ampoule contains the equivalent of 50 mg iron per mL. Pharmacological tests have shown that the complex has a LD50 (intravenous) of >2500 mg iron per kg in white mice.

5.2 Pharmacokinetic properties

After an infusion of 100 mg iron as iron polymaltose in 48 mL 0.9% sodium chloride, at a rate of 1.7 mL/min, a C_{max} (in serum) of 25.1 mcg/mL iron was observed. The terminal half-life was 22.4 hours. The MRT 20.2 hours and the VD (distribution volume) 2.93 litres. Renal elimination is less than 1% of the total dosage.

Iron polymaltose shows a high structural homogeneity and thus steady delivery of the complexed iron to endogenous iron binding proteins.

Taken up from plasma by the reticuloendothelial system (RES), the iron is split off, binds to transferrin and partially re-enters the plasma from where it reaches the bone marrow for haemoglobin synthesis.

Only very small amounts of iron are excreted. The conservation of body iron and the lack of an excretory mechanism for excess iron may lead to iron overload if iron intake is excessive. Polymaltose is either metabolised or excreted.

Further Information

Ferrosig contains a macromolecular spherocolloidal complex of iron(III) hydroxide and the carbohydrate ligand polymaltose. The complex has a molecular weight of about 462,000. The

aqueous colloidal solution is sterile, pyrogen-free and approximates the pH and tonicity of the tissues.

5.3 Preclinical safety data

Not stated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Hydrochloric acid
- Sodium hydroxide
- Water for injection

6.2 Incompatibilities

Not stated, see section 4.5 for interactions with other medicines.

6.3 Shelf life

- 36 months from date of manufacture stored at or below 25°C, protect from light.
- 12 hours diluted, stored at or below 25°C, protect from light.

6.4 Special precautions for storage

Store at or below 25°C protect from light, do not freeze.

6.5 Nature and contents of container

Carton of 5 x 2 mL ampoules.
Each ampoule containing 318 mg iron polymaltose equivalent to 100 mg of iron.

6.6 Special precautions for disposal and other handling

Not stated.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

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(09) 488 0330

9. DATE OF FIRST APPROVAL

31 Jul 2003

10. DATE OF REVISION OF THE TEXT

22 Dec 2020

SUMMARY TABLE OF CHANGES

Date	Details
21 Aug 2018	Updated to the SPC format and to align with the source datasheet.
07 Nov 2018	Updated as per Medsafe request in order to retain IV route (RFI2; 6/11/18; TT50-7005).
22 Dec 2020	Added safety information on Kounis syndrome in Special Warnings (4.4), and foetal bradychardia in Pregnancy (4.6).