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.

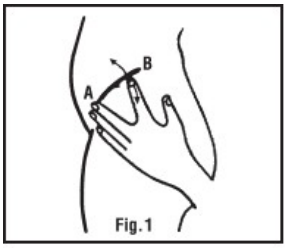

Fig.1

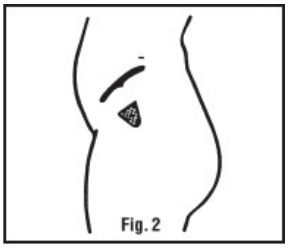
Fig.2

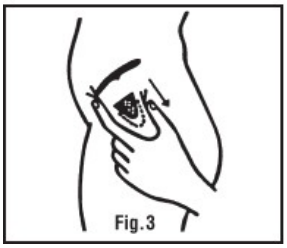
Fig.3

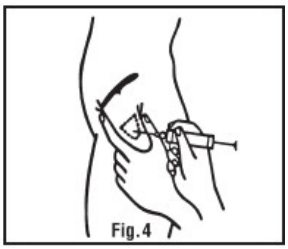
Fig.4

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 and the need for an iron depot of 500mg then:
Hb-iron deficiency = 60 x (150-60) x 0.24 = 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 erythropoiesis, hypoplasia of the marrow)
- Iron overload (e.g. haemochromatosis, haemosiderosis)
- 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

Hypersensitivity and anaphylactoid reactions

There have been reports that hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction).

Parenterally administered iron preparations can cause hypersensitivity reactions including anaphylactoid reactions, which may be potentially fatal. Therefore, facilities for cardiopulmonary resuscitation must be available. If allergic reactions or signs of intolerance occur during administration, the treatment must be stopped immediately.

It is recommended that patients be monitored during and after Ferrosig administration for at least 30 minutes.

Initial test doses may still be carried out, but this is no longer required as a test dose without incident does not indicate that subsequent doses will also be reaction free.

Since parental 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 parental iron therapy exists, confirmed by appropriate laboratory tests.

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. An initial test dose of 25 mg of iron polymaltose should be given prior to the first therapeutic dose of the drug. Adrenaline and facilities for the cardio- pulmonary resuscitation must be available. In the case of a mild allergic reaction, administer antihistamines.

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 a history of allergic disorders, hepatic 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.

Use in the elderly
No data available. For use in elderly, patients should consult a medical practitioner.

Paediatric use
No data available.

Effects on laboratory tests
Refer to Section 4.8.

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 may 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

Effects on fertility
No data available.

Use in pregnancy

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 administration of parenteral irons to pregnant women.

Ferrosig should only be used in pregnancy if the benefits outweigh the risk due to the risk of anaphylaxis.

Ferrosig should not be administered in the first trimester of pregnancy. No controlled studies are available on animals or on pregnant women.

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.

Use in lactation

No data available

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Undesirable effects

Kounis Syndrome – frequency not known.

In pregnancy, associated foetal bradycardia may occur with parenteral iron preparations.

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

Following intramuscular injection

- 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
- Hypophosphataemia including hypophosphataemic osteomalacia

Cardiovascular
- Faintness
- 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.

Laboratory Test Interferences

Large intravenous doses (250 mg or more of iron) of Ferrosig injection may cause serum from blood samples obtained 4 hours after administration of the drug to have a brown colour. The drug may cause falsely elevated values of serum bilirubin and falsely decreased values of serum calcium. Serum iron determinations (especially colorimetric assays) may not be meaningful for 3 weeks following the administration of the drug. Results of serum iron measurements obtained within 1-2 weeks of administration of large doses of the drug should be interpreted with caution.

Examination of the bone marrow for iron stores may not be meaningful for prolonged periods following treatment as Ferrosig injection may remain in the reticuloendothelial cells.

Bone scans with technetium Tc 99m diphosphonate, taken 1-6 days after intramuscular injection of the drug may show dense areas of activity in the buttock, following the contour of the iliac crest. Bone scans using imaging agents labelled with technetium Tc 99m, in the presence of high serum ferritin concentrations or following intravenous infusions of the drug, may show reduced bone uptake, marked renal activity, and excessive blood pool and soft tissue accumulation.

The drug may cause a decrease in Ga-67 gallium citrate uptake during tumor and/or abscess imaging with Ga-67 gallium citrate due to competition for the same binding sites.

The presence of iron may give false-positive orthotolidine test results.

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://pophealth.my.site.com/carmreportnz/s/

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

Mechanism of action

The intended pharmacological action of iron polymaltose is to provide utilisable iron to target tissues. Iron polymaltose delivers iron across enterocytes to the iron transport protein transferrin and the iron storage protein ferritin. This iron is subsequently incorporated into haemoglobin during synthesis of red blood cells and thus facilitates correction of iron deficiency and anaemia.

Clinical trials

No data available

5.2 Pharmacokinetic properties

When injected intramuscularly the iron polymaltose evokes a local inflammatory response and is transported via the lymphatics to the regional lymph nodes without being broken down (reactive absorption). It then enters the blood, reaching its maximum concentration in about 24 hours. The circulating iron polymaltose is taken up by the cells of the reticulo-endothelial system, which slowly ionise it to Fe^{3+} and polymaltose. The majority of Fe^{3+} is bound to transferrin and transported to the bone marrow where it is incorporated into haemoglobin, the remainder is contained within the storage forms, haemosiderin and ferritin, or incorporated into myoglobin or haem-containing enzymes. 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.

A study was conducted on 12 anaemic women aged from 20-45 years. After an intravenous infusion of 100 mg elemental iron, comprising 2 mL of Ferrosig injection diluted in 48 mL 0.9% sodium chloride, at a rate of 1.7 mL/min. (i.e. 50 mL per 30 minutes) a mean C_{max} (in serum) of

25.1 µg/mL iron was observed. The mean T_{max} was 0.75 hours and the mean terminal half-life 22.4 hours. The mean residence time (MRT) was 20.2 hours.

5.3 Preclinical safety data

Genotoxicity
No data available.

Carcinogenicity
No data available.

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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Auckland 0740
(09) 488 0330

9. DATE OF FIRST APPROVAL

31 Jul 2003

10. DATE OF REVISION OF THE TEXT

19 January 2024

SUMMARY TABLE OF CHANGES

Section	Details
4.3	Removed Ostler-Rendu-Weber syndrome as a contraindication.
4.4, 4.6	Update and rearrangement of information under appropriate headings.
4.7	Updated to add further clarification.
4.8	Information updated as follows: • Information added: Kounis Syndrome and foetal bradycardia in pregnancy. • Section updated: Musculoskeletal – Hypophosphataemia. • New section added: Laboratory Test Interferences. • Link updated to report suspected adverse reactions.
5.1, 5.2, 5.3	Information updated.
All	Minor editorial changes.