1. PRODUCT NAME
Ferrosig
Solution for Injection 50mg/mL

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

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

**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 2500mg 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 0.067ml).
  - 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**
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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 = 150g/L, actual Hb 60g/L then:
Iron dose (mg) = 60 x (150-60) x 0.24 + 500mg= 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.

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<th>Body weight kg</th>
<th>Hb 60 g/L</th>
<th>Hb 75 g/L</th>
<th>Hb 90 g/L</th>
<th>Hb 105 g/L</th>
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<tr>
<td></td>
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</tbody>
</table>
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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, megaloblastic 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
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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.

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 haemoglobinopathies.

### 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.

### 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**
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- 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.
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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 Cmax (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
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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
Cartons of 5 x 2mL ampoules, each ampoule containing 318mg iron polymaltose equivalent to 100mg of iron.

6.6 Special precautions for disposal and other handling
Not stated

7. MEDICINE SCHEDULE
Prescription medicine

8. SPONSOR
Multichem NZ Ltd
8 Apollo Drive,
Rosedale 0632
Auckland
(09) 488 0330

9. DATE OF FIRST APPROVAL
31/7/2003

10. DATE OF REVISION OF THE TEXT
21/8/2018

SUMMARY TABLE OF CHANGES

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<td>21/8/2018</td>
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<tr>
<td>07/11/2018</td>
<td>Updated as per Medsafe request in order to retain IV route (RFI2; 6/11/18; TT50-7005)</td>
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