PRODUCT INFORMATION

FERRUM H® Injection

NAME OF THE DRUG

Iron polymaltose

DESCRIPTION

Ferrum H contains a macromolecular spherocolloidal complex of iron(III)-hydroxide and the carbohydrate polymaltose. The complex has a molecular weight of 462,000.

Each 2 mL ampoule of Ferrum H contains the equivalent of 100 mg of iron. The aqueous colloidal solution is sterile, pyrogen-free and approximates the pH and tonicity of the tissues.

The excipients are water for injections, hydrochloric acid and sodium hydroxide (for pH adjustment).

PHARMACOLOGY

Ferrum H is an aqueous, approximately isotonic solution for intramuscular injection.

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 reticuloendothelial 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 Ferrum H 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 $C_{\text{max}}$ (in serum) of 25.1 µg/mL iron was observed. The mean $T_{\text{max}}$ was 0.75 hours and the mean terminal half-life 22.4 hours. The mean residence time (MRT) was 20.2 hours.

INDICATIONS

For the treatment of iron deficiency anaemia in the following circumstances:

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

Ferrum H 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)
– Osler-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.

PRECAUTIONS

*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 parenteral 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 25mg of iron polymaltose should be given prior to the first therapeutic dose of the drug. Adrenaline and facilities for the cardiopulmonary resuscitation must be available. In the case of a mild allergic reaction, administer antihistamines.

Patients with bronchial asthma, low iron binding capacity or folic acid deficiency are particularly at a 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, e.g. those with haemoglobinopathies.

**Use in Pregnancy**

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

Ferrum H should only be administered in the second and third trimester of pregnancy if the benefits of treatment outweigh the potential risk to the foetus.

*Australian categorisation definition of Category A:* Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

**Interactions**

As with all parenteral iron preparations, Ferrum H ampoules 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 angiotensin converting enzyme (ACE) inhibitors may increase the incidence of adverse effects associated with parenteral iron preparations, e.g. erythema, abdominal cramps, nausea, vomiting and hypotension.

**ADVERSE EFFECTS**

Adverse reactions to parenteral Ferrum H 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

**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 Ferrum H injection.

**Laboratory Test Interferences**
Large intravenous doses (250 mg or more of iron) of Ferrum H 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 Ferrum H 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.

**DOSAGE AND ADMINISTRATION**

**Intramuscular Use**

Technique of injection:
*The technique of injection is of crucial importance. Ferrum H 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.

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

b. 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).

c. 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.

d. 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).

e. 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.

f. The patient should move about after the injection.
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, 301–619, 1970):

\[
\text{Iron dose (mg)} = \text{Hb-iron deficiency + iron depot}
\]

\[
\text{Hb-iron deficiency} = \text{body weight (kg)} \times (\text{target HB – actual Hb in g/L}) \times 0.24^* 
\]

* The factor 0.24 = 0.0034 x 0.07 x 1000

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

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 a patient weighing 60 kg, target Hb 150 g/L, actual Hb 60 g/L and the need for an iron depot of 500 mg then:

\[
\text{Hb-iron deficiency} = 60 \times (150-60) \times 0.24 + 500 \text{ mg} = 1296 \text{ mg} + 500 \text{ mg} = 1800 \text{ mg iron.}
\]

Therefore the patient requires 1800 mg iron or 18 ampoules.

Dosage Table

Dosage table for the determination of the total millilitres of Ferrum H injection required

<table>
<thead>
<tr>
<th>Body weight</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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<td>amp.</td>
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<td>21.5</td>
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</tbody>
</table>

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

Overdosage
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.

Opening one point cut ampoules
The following diagrams show the method of opening one point cut ampoules.

POISONS SCHEDULE: S4
Medicine classification
PRESCRIPTION ONLY MEDICINE

PRESENTATION
Cartons of 5 x 2 mL ampoules, with each ampoule containing 100 mg iron (50 mg per mL) as iron polymaltose.

Storage
The ampoules should be stored below 25°C. Do not freeze. Protect from light.

NAME AND ADDRESS OF THE SPONSOR
Aspen Pharmacare Australia Pty Ltd
34-36 Chandos Street
St Leonards NSW 2065
Ferrum H is a product of original research, and is manufactured by Vifor (International) Inc. P.O. Box, 9001 St.Gallen, Switzerland.

Approved by TGA: 22 July 2008