

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

MONOFER[®] (ferric derisomaltose 100 mg/1 mL solution for injection vial)

MONOFER[®] (ferric derisomaltose 200 mg/2 mL solution for injection vial)

MONOFER[®] (ferric derisomaltose 500 mg/5 mL solution for injection vial)

MONOFER[®] (ferric derisomaltose 1000 mg/10 mL solution for injection vial)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ferric derisomaltose is a dark reddish brown powder containing 24% iron (III).

MONOFER solution for injection is available in 100 mg, 200 mg, 500 mg and 1000mg vials containing 1 mL, 2 mL, 5 mL and 10 mL respectively, of ferric derisomaltose 100 mg/1 mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

MONOFER is a sterile, dark brown, non-transparent solution with pH 5.0-7.0 containing ferric derisomaltose dissolved in water for injection. The pH may have been adjusted with hydrochloric acid or sodium hydroxide, and the product is filled under nitrogen gas.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MONOFER is indicated for the treatment of iron deficiency in adults, under the following conditions:

- When oral iron preparations are ineffective or cannot be used
- Where there is a clinical need to deliver iron rapidly

The diagnosis must be based on laboratory tests.

4.2 Dose and method of administration

Monitor patients carefully for signs and symptoms of hypersensitivity reactions during and following each administration of MONOFER. MONOFER should only be administered when staff trained to evaluate and manage anaphylactic reactions are immediately available, in an environment where full resuscitation facilities can be assured. The patient should be observed for adverse effects for at least 30 minutes

following each MONOFER injection (see Section 4.4 Special warnings and precautions for use).

Each IV iron administration is associated with a risk of a hypersensitivity reaction. Thus, to minimise risk the number of single IV iron administrations should be kept to a minimum.

Dosage

Calculation of the cumulative iron need

Iron replacement in patients with iron deficiency:

The dose of MONOFER is expressed in mg of elemental iron. The iron need and the administration schedule for MONOFER must be individually established for each patient. The optimal Hb target level and iron stores may vary in different patient groups and between patients. Please refer to official guidelines.

Iron deficiency anaemia will not appear until essentially all iron stores have been depleted. Iron therapy should therefore replenish both Hb iron and iron stores.

After the current iron deficit has been corrected, patients may require continued therapy with MONOFER to maintain target levels of Hb and acceptable limits of other iron parameters.

The cumulative iron need can be determined using either the Simplified table (1) or the Ganzoni formula (2). It is recommended to use the Ganzoni formula in patients who are likely to require individually adjusted dosing such as patients with anorexia nervosa, cachexia, obesity, pregnancy or anaemia due to bleeding.

1. **Simplified table:**

Table 1: Simplified table

| Hb (g/L) | Patients with bodyweight 50 kg to <70 kg | Patients with body weight ≥70 kg |
|----------|--|----------------------------------|
| ≥100 | 1000 mg | 1500 mg |
| <100 | 1500 mg | 2000 mg |

2. **Ganzoni formula:**

$$\text{Iron need} \begin{matrix} [\text{mg iron}] \\ \text{[mg iron]} \end{matrix} = \text{Body weight}^{(A)} \begin{matrix} [\text{kg}] \\ \text{[kg]} \end{matrix} \times (\text{Target Hb}^{(D)} - \text{Actual Hb})^{(B)} \begin{matrix} [\text{g/L}] \\ \text{[g/L]} \end{matrix} \times 0.24 + \text{Iron for iron stores}^{(C)} \begin{matrix} [\text{mg iron}] \\ \text{[mg iron]} \end{matrix}$$

(A) It is recommended to use the patient's ideal body weight for obese patients or pre-pregnancy weight for pregnant women. For all other patients use actual body weight. Ideal body weight may be calculated in a number of ways e.g. by calculating weight at BMI 25 i.e. ideal body weight = 25 * (height in m)²

(B) To convert Hb [mM] to Hb [g/L] you should multiply Hb [mM] by factor 16.1145

(C) For a person with a body weight above 35 kg, the iron stores are 500 mg or above. Iron stores of 500 mg are at the lower limit normal for small women. Some guidelines suggest using 10-15 mg iron /kg body weight.

- (D) Default Hb target is 150 g/L in the Ganzoni formula. In special cases such as pregnancy consider using a lower Hb target.

The dose-response relationship observed with MONOFER suggests that the true iron demand of IV iron is underestimated by the Ganzoni formula if a Hb target of less than 150 g/L is used.

Method of administration

MONOFER must only be mixed with sterile 0.9 % sodium chloride. No other intravenous dilution solutions should be used. No other therapeutic agents should be added. The diluted solution for injection should be visually inspected prior to use. Use only clear solutions without sediment.

MONOFER must be administered by the intravenous route either by injection or by infusion.

MONOFER should not be administered concomitantly with oral iron preparations, since the absorption of oral iron might be decreased.

Intravenous bolus injection:

MONOFER may be administered as an intravenous bolus injection up to 500 mg up to three times a week at an administration rate of up to 250 mg iron/minute. It may be administered undiluted or diluted in maximum 20 mL sterile 0.9 % sodium chloride.

Table 2: Administration rates for intravenous bolus injection

| Volume of MONOFER | Equivalent iron dose | Administration rate/ Minimum administration time | Frequency |
|-------------------|----------------------|--|------------------|
| ≤5 ml | ≤500 mg | 250 mg iron/minute | 1-3 times a week |

Intravenous infusion:

The cumulative iron need required may be administered in a single MONOFER infusion up to 20 mg iron/kg body weight or as weekly infusions until the cumulative iron need has been administered.

If the cumulative iron need exceeds 20 mg iron/kg body weight, the dose must be split in two administrations with an interval of at least one week. It is recommended whenever possible to give 20 mg iron/kg body weight in the first administration. Dependent on clinical judgement the second administration could await follow-up laboratory tests.

Doses up to 1000 mg must be administered over 20 minutes. Doses exceeding 1000 mg must be administered over 30 minutes or more. Single doses above 1500 mg are not recommended.

Table 3: Administration rates for intravenous infusion

| Iron dose | Minimum administration time |
|-----------|-----------------------------|
| ≤1000 mg | 20 minutes |
| >1000 mg | 30 minutes or more |

MONOFER should be infused undiluted or diluted in sterile 0.9% sodium chloride. For stability reasons, MONOFER should not be diluted to concentrations less than 1 mg iron/mL (not including the volume of the ferric derisomaltose solution) and never diluted in more than 500 mL.

Injection into dialyser:

MONOFER may be administered during a haemodialysis session directly into the venous limb of the dialyser under the same procedures as outlined for intravenous bolus injection.

4.3 Contraindications

- Hypersensitivity to the active substance, to MONOFER or any of the excipients
- Non-iron deficiency anaemia (eg. haemolytic anaemia)
- Iron overload or disturbances in utilisation of iron (e.g. haemochromatosis, haemosiderosis)

4.4 Special warnings and precautions for use

Parenterally administered iron preparations can cause hypersensitivity reactions including serious and potentially fatal anaphylactic/anaphylactoid reactions. Hypersensitivity reactions have also been reported after previously uneventful doses of parenteral iron complexes. There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction).

The risk is enhanced for patients with known allergies including drug allergies, previous severe hypersensitivity to other parenteral iron products, and including patients with a history of severe asthma, eczema or other atopic allergy.

There is also an increased risk of hypersensitivity reactions to parenteral iron complexes in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis).

MONOFER should only be administered when staff trained to evaluate and manage anaphylactic reactions are immediately available, in an environment where full resuscitation facilities can be assured. Each patient should be observed for adverse effects for at least 30 minutes following each MONOFER injection. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Facilities for cardio respiratory resuscitation and equipment for handling acute anaphylactic/anaphylactoid reactions should be available, including an injectable 1:1000 adrenaline solution. Additional supportive treatment should be given as appropriate.

In patients with compensated liver dysfunction, parenteral iron should only be administered after careful benefit/risk assessment. Parenteral iron administration should be avoided in patients with hepatic dysfunction (alanine aminotransferase and/or aspartate aminotransferase > 3 times upper limit of normal) where iron overload is a precipitating factor, in particular Porphyria Cutanea Tarda (PCT). Careful monitoring of iron status is recommended to avoid iron overload.

Parenteral iron must be used with caution in case of acute or chronic infection. In patients with chronic infection a risk/benefit evaluation has to be performed, taking into account the suppression of erythropoiesis.

MONOFER should not be used in patients with ongoing bacteraemia.

Hypotensive episodes may occur if intravenous injection is administered too rapidly.

Caution should be exercised to avoid paravenous leakage when administering MONOFER. Paravenous leakage of MONOFER at the injection site may lead to irritation of the skin and potentially long lasting brown discolouration at the site of injection. In case of paravenous leakage, the administration of MONOFER must be stopped immediately. Distant skin discolouration has also been reported.

Use in the elderly

No specific adjustment is required for use in the elderly.

A careful risk benefit assessment is required before parenteral iron is used in patients aged > 65 years and close monitoring for adverse events is required.

Paediatric population

Ferric derisomaltose is not recommended for use in children and adolescents < 18 years due to insufficient data on safety and efficacy.

Effects on laboratory tests

Parenteral iron may cause falsely elevated values of serum bilirubin and falsely decreased values of serum calcium.

4.5 Interaction with other medicines and other forms of interaction

As with all parenteral iron preparations the absorption of oral iron is reduced when administered concomitantly.

Large doses of parenteral iron (5 mL or more) have been reported to give a brown colour to serum from a blood sample drawn four hours after administration.

4.6 Fertility, pregnancy and lactation

Fertility

There are no data on the effect of ferric derisomaltose on human fertility.

In a fertility study with ferric derisomaltose in rats no effects on female fertility or male reproductive performance and spermatogenic parameters were found at the dose levels tested.

Ferric derisomaltose did not affect fertility in male or female rats when administered IV at up to 19 mg/kg/day in males and 32 mg/kg/day in females (4 and 7 times the maximum recommended weekly clinical dose, respectively). Atrophy of prostate and seminal vesicles, seminiferous epithelium degeneration of testes, and degenerative germ cells in epididymides were observed in rats at 80 mg/kg/day thrice weekly (8 times the maximum recommended weekly clinical dose).

Pregnancy

Category B3

There are no adequate and well-controlled trials of ferric derisomaltose in pregnant women. A careful risk/benefit evaluation is therefore required before use during pregnancy and ferric derisomaltose should not be used during pregnancy unless clearly necessary.

Iron deficiency anaemia occurring in the first trimester of pregnancy can in many cases be treated with oral iron. Treatment with ferric derisomaltose should be confined to the second and third trimester if the benefit is judged to outweigh the potential risk for both the mother and the fetus.

Fetal 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 intravenous administration of parenteral irons to pregnant women.

Iron complexes have been reported to be teratogenic and embryocidal in non-anaemic pregnant animals at high single doses above 125 mg iron/kg body weight. The highest recommended dose in clinical use is 20 mg iron/kg body weight.

In embryofetal development studies in rats and rabbits, there was a dose-dependent increase in bent ribs in rats at all doses (3-32 mg/kg/day, 0.7-8 times the maximum recommended weekly clinical dose) and fetal malformations (including hydrocephaly, microglossia, narrow pectoral region) in rabbits at ≥ 25 mg/kg/day (≥ 6 times the maximum recommended weekly clinical dose). There was a significant reduction in viable fetuses and mean fetal weight and an increase in late resorption in rabbits at 43 mg/kg/day (10 times the maximum recommended weekly clinical dose).

Lactation

No formal clinical studies investigating excretion of ferric derisomaltose have been performed. In clinical study P-PP-01, a maternal milk sample was collected on day 3 from a total of 65 subjects. Overall, mean maternal milk iron level was higher in the iron isomaltoside 1000 group (0.000721 g/L) than in the standard medical care group (0.000400 g/L) at day 3. However, at week 1 the mean maternal milk iron level in the iron isomaltoside 1000 group had decreased to the same level as in the standard medical care group (0.000468 g/L and 0.000442 g/L, respectively).

4.7 Effects on ability to drive and use machinery

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

The table presents the adverse drug reactions (ADRs) reported during MONOFER treatment in clinical trials and in-market experience.

Acute severe hypersensitivity reactions may occur with parenteral iron preparations. They usually occur within the first few minutes of administration and are generally characterised by the sudden onset of respiratory difficulty and/or

cardiovascular collapse; fatalities have been reported. Other less severe manifestations of immediate hypersensitivity, such as urticaria and itching may also occur. In pregnancy, associated fetal bradycardia may occur with parenteral iron preparations.

Fishbane reaction characterised by flushing in the face, acute chest and/or back pain and tightness sometimes with dyspnoea in association with intravenous iron treatment may occur (frequency uncommon). This may mimic the early symptoms of an anaphylactoid/anaphylactic reaction. The infusion should be stopped and the patient's vital signs should be assessed. These symptoms disappear shortly after the iron administration is stopped. They typically do not reoccur if the administration is restarted at a lower infusion rate.

Distant skin discolouration has also been reported post marketing following IV iron administration.

Adverse drug reactions observed during clinical trials and post-marketing experience

| System Organ Class | Common (≥1/100 to <1/10) | Uncommon (≥1/1000 to <1/100) | Rare (≥1/10000 to <1/1000) | Not known |
|--|--------------------------|---|---|-----------------------------|
| Immune system disorders | | Hypersensitivity, including severe reactions | Anaphylactoid/anaphylactic reactions | |
| Nervous system disorders | | Headache paraesthesia, dysgeusia, blurred vision, loss of consciousness, dizziness, fatigue | Dysphonia, seizure, tremor, altered mental status | |
| Cardiac disorders | | Tachycardia | Arrhythmia, palpitations | Kounis syndrome |
| Vascular disorders | | Hypotension, hypertension | | |
| Respiratory, thoracic and mediastinal disorders | | Chest pain, dyspnoea, bronchospasm | | |
| Gastrointestinal disorders | Nausea | Abdominal pain, vomiting, dyspepsia, constipation, diarrhoea | | |
| Skin and subcutaneous tissue disorders | Rash | Pruritus, urticaria, flushing, sweating, dermatitis | Angioedema | Distant skin discolouration |
| Metabolism and nutritional disorders | | Hypophosphataemia | | |

| System Organ Class | Common (≥1/100 to <1/10) | Uncommon (≥1/1000 to <1/100) | Rare (≥1/10000 to <1/1000) | Not known |
|---|----------------------------|--|------------------------------------|-----------|
| Musculoskeletal and connective tissue disorders | | Back pain, myalgia, arthralgia, muscle spasms | | |
| General disorders and administration site conditions | Injection site reactions * | Pyrexia, chills/shivering, infection, local phlebitic reaction, swelling, pain, skin exfoliation | Malaise, influenza like illness ** | |
| Investigations | | Hepatic enzyme increased | | |

* Includes the following preferred terms, i.e. injection site erythema, -swelling, -burning, -pain, -bruising, -discolouration, -extravasation, -irritation, -reaction.

** Influenza like illness whose onset may vary from a few hours to several days

Description of selected adverse reactions

Delayed reactions may also occur with parenteral iron preparations and can be severe. They are characterised by arthralgia, myalgia and sometimes fever. The onset varies from several hours up to four days after administration. Symptoms usually last two to four days and settle spontaneously or following the use of simple analgesics.

Post-marketing experience

Post marketing adverse reactions are included in the above table.

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

The ferric derisomaltose in MONOFER has a low toxicity. The preparation is well tolerated and has a minimal risk of accidental overdosing.

Overdose may lead to accumulation of iron in storage sites eventually leading to haemosiderosis. Monitoring of iron parameters such as serum ferritin may assist in recognising iron accumulation. Supportive measures such as chelating agents can be used

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

Pharmacotherapeutic group: Iron parenteral preparation, ATC code: B03AC

The MONOFER formulation contains iron in a complex with derisomaltose that releases bioavailable iron to iron-binding proteins.

Although iron is the active compound in all parenteral iron preparations, ferric derisomaltose is different from other IV iron complexes such as iron dextran and ferric carboxymaltose. IV iron complexes are not clinically interchangeable.

The iron is available in a non-ionic water-soluble form in an aqueous solution with pH between 5.0 and 7.0.

Evidence of a therapeutic response can be seen within a few days of administration of ferric derisomaltose as an increase in the reticulocyte count. Due to the release of bioavailable iron serum ferritin peaks within days after an intravenous dose of MONOFER and slowly returns to baseline after weeks.

Clinical efficacy

The efficacy of MONOFER has been studied in the different therapeutic areas necessitating intravenous iron to correct iron deficiency. The main trials are described in more detail below.

Iron deficiency anaemia outside CKD

The IDA-01 trial was an open-label, comparative, randomised, multi-centre, non-inferiority trial conducted in 511 patients with IDA randomised 2:1 to either MONOFER or iron sucrose. 90 % of recruited patients were females. The dosing of MONOFER was performed according to the Simplified table as described under Dose and method of administration and dosing of iron sucrose was calculated according to Ganzoni and administered as 200 mg infusions. The primary endpoint was the proportion of patients with an Hb increase ≥ 20 g/L from baseline at any time between weeks 1 to 5. A higher proportion of patients treated with MONOFER compared to iron sucrose reached the primary endpoint, 68.5 % vs 51.6 %, respectively (Full Analysis Set (FAS), $p < 0.0001$).

The IDA-03 trial was an open-label, comparative, randomised, multi-centre trial conducted in 1512 patients with IDA randomised 2:1 to either MONOFER 1000 mg infused over 20 min (1009 subjects) or iron sucrose administered as 200 mg IV injections repeated up to a cumulative dose of 1000 mg (503 subjects). For the co-primary efficacy endpoint the change from baseline to week 8 in Hb was 24.9 g/L in the MONOFER group and 24.9 g/L in the iron sucrose group. The estimated treatment difference [95 % CI] of MONOFER - iron sucrose was 0.0 g/L [-1.3;1.3]. Since the lower bound of the 95 % CI for the treatment difference was above -5 g/L, non-inferiority was concluded. For the co-primary safety endpoint, a total of 3 treatment emergent serious or severe hypersensitivity reactions in 989 subjects (0.3 %) were adjudicated and confirmed by the adjudication committee in the MONOFER group. The 95 % CI was [0.06 %;0.88 %] and as the upper bound was < 3 %, the primary safety objective was considered met. In the iron sucrose group 2 treatment emergent serious or severe hypersensitivity reactions in 494 subjects (0.4 %) were

adjudicated and confirmed by the adjudication committee. The risk difference between MONOFER and iron sucrose was estimated to -0.10 % [95% CI: -0.91;0.71].

Nephrology

Non-dialysis-dependent chronic kidney disease

The CKD-02 trial was an open-label, comparative, randomised, multi-centre, non-inferiority trial conducted in 351 iron deficient non-dialysis dependent (NDD) chronic kidney disease (CKD) patients, randomised 2:1 to either MONOFER or oral iron sulphate administered as 100 mg elemental oral iron twice daily (200 mg daily) for 8 weeks. The patients in the MONOFER group were randomised to infusion of 1000 mg single doses or bolus injections of 500 mg. The test for non-inferiority showed that MONOFER was non-inferior to iron sulphate in its ability to increase Hb from baseline to week 4 in both FAS and PP datasets (FAS: difference estimate: 0.2216, 95 % CI: 0.012:0.431, $p < 0.0001$; PP: difference estimate: 0.2176, 95 % CI: 0.003:0.432, $p < 0.0001$) and also sustained a superior increase in Hb compared to oral iron from week 3 until the end of trial at week 8 ($p=0.009$ at week 3, $p=0.04$ at week 4, $p=0.0004$ at week 8, FAS).

The CKD-04 trial was an open-label, comparative, randomised, multi-centre trial conducted in 1538 NDD-CKD patients with IDA randomised 2:1 to either MONOFER 1000 mg infused over 20 min (1027 subjects) or iron sucrose administered as 200 mg IV injections repeated up to a cumulative dose of 1000 mg (511 subjects). For the co-primary efficacy endpoint, the change from baseline to week 8 in Hb was 12.2 g/L in the MONOFER group and 11.4 g/L in the iron sucrose group. The estimated treatment difference was 0.8 g/L [95% CI: -0.6;2.3]. Since the lower bound of the 95 % CI was above -5 g/L, non-inferiority was concluded. For the co-primary safety endpoint, a total of 3 treatment emergent serious or severe hypersensitivity reactions in 1019 subjects (0.3 %) were adjudicated and confirmed by the adjudication committee in the MONOFER group. The 95 % CI was [0.06 %;0.86 %] and as the upper bound was <3 %, the primary safety objective was considered met. No treatment emergent serious or severe hypersensitivity reactions were adjudicated and confirmed by the adjudication committee in the iron sucrose group. The risk difference between MONOFER and iron sucrose was estimated to 0.29 % [95% CI: -0.19;0.77].

Haemodialysis-dependent chronic kidney disease

The CKD-03 trial was an open-label, comparative, randomised, multi-centre, non-inferiority trial conducted in 351 haemodialysis patients randomised 2:1 to either MONOFER or iron sucrose. Patients were randomised to either a single injection of 500 mg or 500 mg in split doses of MONOFER or 500 mg iron sucrose in sp In the FAS of 341 subjects, a total of 187 (82.7 %) subjects treated with ferric derisomaltose and 95 (82.3 %) subjects treated with iron sucrose were able to maintain Hb between 95 and 125 g/L.

Oncology

Cancer related anaemia

The CIA-01 trial was an open-label, comparative, randomised, multi-centre, non-inferiority trial conducted in 350 cancer patients with anaemia randomised 2:1 to

either MONOFER or oral iron sulphate administered as 100 mg elemental oral iron twice daily (200 mg daily) for 12 weeks. The patients in the MONOFER group were randomised to either an infusion of max 1000 mg single doses or bolus injections of 500 mg. The primary endpoint was change in Hb concentrations from baseline to week 4. The test for non-inferiority showed that MONOFER was non-inferior to iron sulphate in its ability to increase Hb from baseline to week 4 in both FAS and PP datasets (FAS: difference estimate: 0.0161, 95 % CI: -0.261:0.293, $p = 0.0002$; PP: difference estimate: -0.0071, 95 % CI: -0.291:0.276, $p = 0.0006$).

Gastroenterology

Inflammatory bowel disease

The IBD-01 trial was an open-label, comparative, randomised, multi-centre, non-inferiority trial conducted in 338 inflammatory bowel disease (IBD) patients (mild to moderate disease severity) randomised 2:1 to receive either MONOFER or oral iron sulphate administered as 100 mg elemental oral iron twice daily for 8 weeks (200 mg daily). The patients in the MONOFER group were randomised to either an infusion of max 1000 mg single doses or bolus injections of 500 mg. The primary endpoint was change in Hb concentrations from baseline to week 8. A modified Ganzoni formula was used to calculate the IV iron need with a target Hb of only 130 g/L. Non-inferiority could not be statistically demonstrated on the primary endpoint (FAS: $p = 0.0945$). The study demonstrated an increase in Hb concentration from a mean of 96.4 g/L at baseline to 122.3 g/L at week 8 in subjects treated with MONOFER and an increase from 96.1 g/L at baseline to 125.9 g/L at week 8 in subjects treated with oral iron sulphate. The dose-response relationship observed with MONOFER suggests that the true iron demand of IV iron was underestimated by the modified Ganzoni formula.

Post-partum haemorrhage

The PP-01 trial was an open-label, comparative, randomised, single-centre trial conducted in 200 healthy women with postpartum haemorrhage (PPH) exceeding 700 mL and ≤ 1000 mL or PPH >1000 mL and Hb >65 g/L measured >12 hours after delivery. The women were randomised 1:1 to receive either a single dose of 1200 mg MONOFER or standard medical care (i.e the majority of patients were prescribed oral iron). The primary endpoint was the aggregated change in physical fatigue within 12 weeks postpartum. The difference in aggregated change in physical fatigue score within 12 weeks postpartum was -0.97 ($p=0.006$), in favour of MONOFER, although the estimated treatment difference was less than the pre-defined minimum clinically relevant difference of 1.8 required for claiming superiority.

Surgery

Non-anaemic patients undergoing cardiac surgery

The CABG-01 trial was a double-blind, placebo-controlled, randomised, single-centre trial of 60 non-anaemic patients undergoing cardiac surgery (coronary artery bypass graft). The patients were randomized 1:1 to either 1000 mg MONOFER administered perioperatively by infusion or placebo. The primary endpoint was to assess the change in Hb concentrations from baseline to 4 weeks postoperatively. One month after surgery, haemoglobin concentration had increased to an average of 126 g/L versus 118 g/L ($p=0.012$) and significantly more patients were non-anaemic in the MONOFER treated group compared to the placebo group (38.5 % versus 8.0%; $p=0.019$).

5.2 Pharmacokinetic properties

There is no data investigating the pharmacokinetics of single and multiple doses of MONOFER above 1000 mg.

Ferric derisomaltose displays inter-patient variability in PK parameters, including AUC and T_{max} .

Distribution

Following intravenous administration, ferric derisomaltose or released free iron is taken up by the cells of the reticuloendothelial system (RES), particularly in the liver and spleen, from where iron is slowly released.

Metabolism

Circulating iron is removed from the plasma by cells of the RES. The iron binds available protein moieties to form hemosiderin or ferritin, the physiological storage forms of iron, or to a lesser extent, the transport molecule transferrin. This iron, which is subject to physiological control, replenishes haemoglobin (Hb) and depleted iron stores.

Excretion

After administration of a single dose of ferric derisomaltose of 100 to 1000 mg of iron in the pharmacokinetic studies, the iron injected or infused was cleared from the plasma with a half-life that ranged from 1 to 4 days. Renal elimination of iron was negligible.

Iron is not easily eliminated from the body and accumulation can be toxic. Due to the size of the complex, ferric derisomaltose is not eliminated via the kidneys. Small quantities of iron are eliminated in urine and faeces.

Isomaltoside 1000 is either metabolised or excreted.

5.3 Preclinical safety data

Genotoxicity

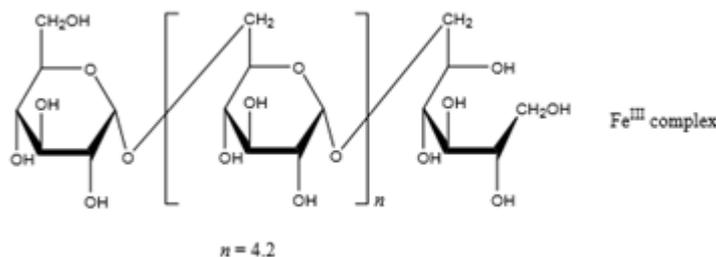
Ferric derisomaltose was not genotoxic in a bacterial mutation assay, a chromosomal aberration test in human lymphocytes *in vitro* or a micronucleus assay in mice *in vivo*.

Carcinogenicity

Carcinogenicity studies were not conducted.

6. PHARMACEUTICAL PARTICULARS

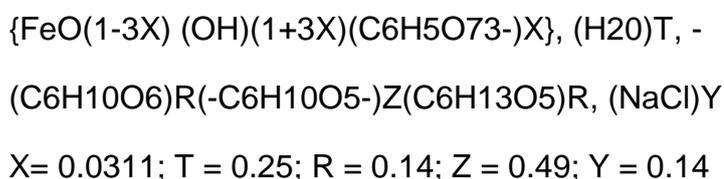
Chemical structure



Chemical name: Iron (III) hydroxide isomaltoside 1000

Synonyms: iron isomaltoside, iron isomaltooligosaccharide, iron oligosaccharide, iron isomaltopentaoside, (1→6)- α -D-glucopyranan-(1→6)-D-glucitol iron(III) complex.

Molecular Formula:



MONOFER solution for injection is a colloid with iron in spheroidal iron-carbohydrate particles.

The MONOFER formulation contains iron in a complex that enables a controlled and slow release of bioavailable iron to iron-binding proteins with little risk of free iron.

Each particle consists of a matrix of iron(III) atoms and derisomaltose with an average molecular weight of 1000 Da and a narrow molecular weight distribution that is almost devoid of mono- and disaccharides. INN name: Ferric derisomaltose (also known as iron(III) isomaltoside 1000).

The chelation of iron(III) with carbohydrate confers to the particles a structure resembling ferritin that is suggested to protect against the toxicity of unbound inorganic iron(III).

The iron is available in a non-ionic water-soluble form in an aqueous solution with pH between 5.0 and 7.0.

This unit has a molecular weight of 235 g/mole - the molecular weight of the colloid particle is approximately 165 kDa hence the colloid particle contains approximately 700 repeatable units (165,000/235).

CAS number

1345510-43-1

6.1 List of excipients

- Water for injections

- Sodium hydroxide
- Hydrochloric acid

6.2 Incompatibilities

MONOFER must only be mixed with sterile 0.9 % sodium chloride. No other intravenous dilution solutions should be used. No other therapeutic agents should be added.

6.3 Shelf life

3 years when stored below 30°C.

Shelf life after dilution with sterile 0.9% sodium chloride: Diluted solutions should be used immediately.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

MONOFER iron (as ferric derisomaltose) 100 mg/1 mL solution for injection vial.
Pack sizes: 1, 5 or 10 x 1 mL.

MONOFER iron (as ferric derisomaltose) 200 mg/2 mL solution for injection vial.
Pack sizes: 5 or 10 x 2 mL.

MONOFER iron (as ferric derisomaltose) 500 mg/5 mL solution for injection vial.
Pack sizes: 1, 2 or 5 x 5 mL.

MONOFER iron (as ferric derisomaltose) 1000 mg/10 mL solution for injection vial.
Pack sizes: 1, 2 or 5 x 10 mL.

MONOFER is supplied in a single use Type 1 glass vial with chlorobutyl rubber stopper and aluminium cap.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

MONOFER is for single use in one patient only. Discard any residue.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

A. Menarini New Zealand Pty Limited
PO Box 90296
Victoria Street West
Auckland 1142 New Zealand
Telephone: Toll free 0800 102 349

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
27 August 2020.

10. DATE OF REVISION OF THE TEXT

01 December 2023.

® Registered trademark

Summary table of changes

| Section changed | Summary of new information |
|-----------------|--|
| 8 | Update Sponsor name, address and contact details |