CLEAN PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

Monofer 100 mg parenteral solution for injection/infusion

Monofer 500 mg parenteral solution for injection/infusion

Monofer 1 000 mg parenteral solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Monofer 100 mg: 1 ml vial/ampoule contains 100 mg iron as ferric derisomaltose.

Monofer 500 mg: 5 ml vial/ampoule contains 500 mg iron as ferric derisomaltose.

Monofer 1 000 mg: 10 ml vial/ampoule contains 1 000 mg iron as ferric derisomaltose.

One ml of solution contains 100 mg iron as ferric derisomaltose.

Monofer contains no preservatives.

Contains sugar: Approximately 20% w/v derisomaltoside.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion.

Monofer 100 mg is a dark brown solution with no signs of precipitation filled into a 1 ml clear glass vial or ampoule.

Monofer 500 mg is a dark brown solution with no signs of precipitation filled into a 5 ml clear glass vial or ampoule.

Monofer 1 000 mg is a dark brown solution with no signs of precipitation filled into a 10 ml clear glass vial or ampoule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Monofer is indicated for the treatment of iron deficiency in 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 Posology and method of administration

Monofer should only be administered when staff trained to evaluate and manage anaphylactic reactions is 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).

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.

Calculation of the cumulative iron dose needed:

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 haemoglobin 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 haemoglobin iron and iron stores.

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

The cumulative iron need can be determined using either the Ganzoni formula (1) or the table below (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.

Haemoglobin is abbreviated Hb:

1. Ganzoni formula:

Iron need = Body weight$^{(A)}$ x (Target Hb$^{(E)}$ - Actual Hb)$^{(B)}$ x 2,4$^{(C)}$ +Iron for iron stores$^{(D)}$

[mg iron] [kg] [g/dl] [mg iron]

(A) It is recommended to use the patient's ideal body weight for obese patients or pre-pregnancy weight for pregnant women. 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/dl] you should multiply Hb [mM] by factor 1,61145

(C) Factor 2,4 = 0,0034 x 0,07 x 10 000

0,0034: Iron content of haemoglobin is 0,34 %

0,07: Blood volume 70 ml/kg of body weight ≈ 7 % of body weight

10 000: The conversion factor 1 g/dl = 10 000 mg/l

(D) 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 and others 1000 mg iron as stores.

(E) Default Hb target is 15 g/dl in the Ganzoni formula. In special cases such as pregnancy consider using a lower haemoglobin target.

2. Simplified table:

Iron need

Hb (g/dl)	Patients with ~~a~~ bodyweight 50 kg to < 70 kg	Patients with ~~a~~ bodyweight ≥ 70 kg
≥ 10	1 000 mg	1 500 mg
< 10	1 500 mg	2 000 mg

The treatment effect should be monitored by blood tests. To reach the target Hb-level, the cumulative iron dose may need adjustment.

Iron replacement for blood loss

Iron therapy in patients with blood loss should supply an amount of iron equivalent to the amount of iron represented in the blood loss.

- If the Hb level is reduced: Use the Ganzoni formula considering that the depot iron does not need to be restored:

  Iron need = Body weight x (Target Hb - Actual Hb) x 2,4

  [mg iron] [kg] [g/dl]

- If the volume of blood lost is known: The administration of 200 mg Monofer results in an increase of haemoglobin which is equivalent to 1 unit blood:

  Iron to be replaced = Number of units blood lost x 200

  [mg iron]

Administration

Monitor patients carefully for signs and symptoms of hypersensitivity reactions during and following each administration of Monofer.

Children and adolescents:

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

Monofer should not be administered concomitantly with oral iron preparations since the absorption of oral iron might be decreased (see section 4.5).

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.

Intravenous drip infusion

The cumulative iron dose 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 dose has been administered.

If the cumulative iron dose 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 1 000 mg must be administered over 15 minutes or more.

Doses exceeding 1 000 mg must be administered over 30 minutes or more.

Monofer should be added to maximum 500 ml sterile 0,9 % sodium chloride (see section 6.4).

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 ferric derisomaltose or to any of the excipients of Monofer (see section 6.1).
- Known serious hypersensitivity to other parenteral iron products.
- Non-iron deficiency anaemia (e.g. haemolytic anaemia).

- Iron overload or disturbances in utilisation of iron (e.g. haemochromatosis, haemosiderosis).
- Monofer should not be used in patients with ongoing bacteraemia.

4.4 Special warnings and precautions for use

Parenterally administered iron preparations such as Monofer, can cause hypersensitivity reactions, including serious and potentially fatal anaphylactic/anaphylactoid reactions. Hypersensitivity reactions have also been reported after previously uneventful doses of other parenteral iron complexes.

The risk is enhanced for patients with known allergies including medicine allergies, including patients with a history of severe asthma, eczema or other atopic allergy.
There is also an increased risk of hypersensitivity reactions to Monofer in patients with immune or inflammatory conditions (e.g., systemic lupus erythematosus, rheumathoid arthritis).

Monofer should only be administered when staff trained to evaluate and manage anaphylactic reactions is 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 epinephrine (adrenaline) solution. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.

In patients with liver impairment, Monofer should only be administered after careful benefit/risk assessment. Monofer administration should be avoided in patients with hepatic impairment (alanine aminotransferase (ALAT) and/or aspartate aminotransferase (ASAT) > 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.

Monofer should be used with caution in cases of acute or chronic infection.

Hypotensive episodes may occur especially if the intravenous injection of Monofer is administered too rapidly.

Caution should be exercised to avoid paravenous leakage when administrating Monofer. Paravenous leakage of Monofer at the injection site may lead to irritation of the skin and long lasting brown discolouration at the site of injection. In case of paravenous leakage, the administration of Monofer must be stopped immediately.

4.5 Interaction with other medicines and other forms of interaction

The absorption of oral iron is reduced when administered concomitantly with Monofer. Oral iron therapy should not be started earlier than 5 days after the last injection of Monofer.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There is only limited data from the use of Monofer in pregnant women from one study with 100 exposed women. A careful risk/benefit evaluation is required before use during pregnancy and Monofer should not be used during pregnancy unless clearly necessary.

Iron deficiency anaemia occurring in the first trimester of pregnancy can in most cases be treated with oral iron. Treatment with Monofer 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 foetus.

Foetal bradycardia may occur following administration of parenteral irons. It is usually transient and a consequence of a hypersensitivity reaction in the mother.

Breastfeeding

A clinical study showed that transfer of iron from Monofer to human milk was very low. At therapeutic doses of Monofer no effects on the breastfeed newborns/infants are anticipated. Women using Monofer should not breastfeed their infants.

Fertility

There are no data on the effect of Monofer on human fertility. Fertility was unaffected following treatment in animal studies. (see section 5.3)

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

a. Summary of the safety profile

The table presents ~~T~~the adverse drug reactions (ADRs) reported during Monofer treatment in clinical trials and during post-marketing experience.

Acute, severe hypersensitivity reactions may occur with Monofer. They usually occur within the first few minutes of administration and are 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 foetal bradycardia may occur with parenteral iron preparations, including Monofer.

Fishbane reaction characterised by flushing in the face, acute chest and/or back pain and tightness sometimes with dyspnoea in association with IV iron treatment may occur. 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 may 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.

b. Tabulated summary of adverse reaction

System organ class	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥1/1 000 to <1/100)**	**Rare (≥ 1/10 000 to < 1/1 000)**	**Not Known**
Immune system disorders		Hypersensitivity, including severe reactions	Anaphylactoid reactions, 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,	
Vascular disorders		Hypotension,		

System organ class	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥1/1 000 to <1/100)**	**Rare (≥ 1/10 000 to < 1/1 000)**	**Not Known**
		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 nutrition disorders		Hypo-phosphataemia		
Musculoskeletal and connective tissue disorders		Back pain, myalgia, arthralgia,		

System organ class	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥1/1 000 to <1/100)**	**Rare (≥ 1/10 000 to < 1/1 000)**	**Not Known**
		muscle spasms		
General disorders and administration site conditions	Injection site reactions*	Pyrexia, chills/shivering, infection, local phlebitic reaction, skin exfoliation	Malaise, influenza like illness **	
Investigations		Hepatic enzyme increased		

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

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

c. <u>Description of selected adverse reactions</u>

Delayed reactions may also occur with Monofer 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 may last two to four days.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

SAHPRA: https://www.sahpra.org.za/Publications/Index/8

Acino Pharma (Pty) Ltd: **E-mail:** drugsafety_ZA@acino.swiss **Tel:** 060 998 7896

4.9 Overdose

Overdose may lead to accumulation of iron in storage sites 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.

Treatment of overdose

Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.8.3 Erythropoietics (Haematinics)

Pharmacotherapeutic group: Iron parenteral preparation, ATC code: B03AC.

Monofer solution for injection is a colloid with strongly bound iron in spheroidal iron-carbohydrate particles.

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.

The iron is available in a non-ionic water-soluble form in an aqueous solution with pH between 5,0 and 7,0.

Due to the slow release of bioavailable iron serum ferritin peaks within days after an intravenous dose of Monofer and slowly returns to baseline after weeks.

5.2 Pharmacokinetic properties

The formulation contains iron in a strongly bound complex that enables a slow release of bioavailable iron to iron-binding proteins with little risk of free iron toxicity.

After administration of a single dose of Monofer of 100 to 1 000 mg of iron in 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.

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

Circulating iron is removed from the plasma by cells of the reticuloendothelial system which split the complex into its components of iron and derisomaltose.

The iron is immediately bound to the available protein moieties to form hemosiderin or ferritin, the physiological storage forms of iron, or to a lesser extent, to the transport molecule transferrin. This iron, which is subject to physiological control, replenishes haemoglobin and depleted iron stores.

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

Derisomaltose is either metabolised or excreted.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)

Water for injection

6.2 Incompatibilities

Monofer must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

3 years

Shelf life after first opening of the container (undiluted)

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

Shelf life after dilution with sterile 0,9 % sodium chloride

Chemical and physical in-use stability has been demonstrated for 48 hours at 30 °C in dilutions up to 1:250 = (0,4 mg/ml) with sterile 0,9 % sodium chloride.

From a microbiological point of view, the product should be used immediately.

6.4 Special precautions for storage

Store at or below 30 °C.

Store in the outer carton until required for use.

6.5 Nature and contents of container

Monofer 100 mg: Packed into a clear 1 ml glass ampoule with a break point or into a clear 1 ml glass

vial sealed with chlorobutyl rubber stopper and aluminium cap with white flip-off button. 5 vials or ampoules packed into an outer carton.

Monofer 500 mg: Packed into a clear 5 ml glass ampoule with a break point or into a clear 5 ml glass vial sealed with chlorobutyl rubber stopper and aluminium cap with white flip-off button. 5 vials or ampoules packed into an outer carton.

Monofer 1000 mg: Packed into a clear 10 ml glass ampoule with a break point or into a clear 10 ml glass vial sealed with chlorobutyl rubber stopper and aluminium cap with white flip-off button. 2 vials or ampoules packed into an outer carton.

6.6 Special precautions for disposal and other handling

Inspect vials/ampoules visually for sediment and damage before use. Use only those containing sediment-free, homogeneous solution.

Monofer is for single use only and any unused solution should be disposed of in accordance with local requirements.

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.

For dilution instructions, see section 4.2.

The reconstituted solution for injection should be visually inspected prior to use. Use only clear solutions without sediment be included.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Acino Pharma (Pty) Ltd

106 16th Road

MIDRAND 1685.

8 REGISTRATION NUMBERS

Monofer 100 mg: 46/8.3/0166

Monofer 500 mg: 46/8.3/0167

Monofer 1 000 mg: 46/8.3/0168

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first approval: 08 April 2019

10 DATE OF REVISION OF THE TEXT

20 October 2023