SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Monofer 100 mg/ml solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One millilitre of solution contains 100 mg iron as iron(III) isomaltoside 1000.

1 ml vial/ampoule contains 100 mg iron as iron(III) isomaltoside 1000

2 ml vial/ampoule contains 200 mg iron as iron(III) isomaltoside 1000

5 ml vial/ampoule contains 500 mg iron as iron(III) isomaltoside 1000

10 ml vial/ampoule contains 1,000 mg iron as iron(III) isomaltoside 1000

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion.

Dark brown, non transparent solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Monofer is indicated for the treatment of iron deficiency anaemia 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 of iron deficiency anaemia should be based on appropriate laboratory tests (e.g. serum ferritin, serum iron, transferrin saturation or hypochromic red cells).

4.2 Posology and method of administration

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 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.
(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 bodyweight 50 kg to <70 kg	Patients with body weight ≥70 kg
≥10	1000 mg	1500 mg
<10	1500 mg	2000 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 carefully patients 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 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.

Children and adolescents:

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

Adults and the elderly:

Monofer can be administered either as an intravenous bolus injection, as an intravenous drip infusion or as a direct injection into the venous limb of the dialyser.

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 1000 mg must be administered over more than 15 minutes.
Doses exceeding 1000 mg must be administered over 30 minutes or more.

Monofer should be added to maximum 500 ml sterile 0.9% sodium chloride. Please refer to section 6.3 and 6.6.

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 its excipients listed in 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)
- Decompensated liver disease

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.

The risk is enhanced for patients with known allergies including drug allergies, 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 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 adrenaline solution. Additional treatment with antihistamines and/or corticosteroids 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 should be used with caution in case of acute or chronic infection.

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 administrating 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.

4.5 Interaction with other medicinal products and other forms of interaction

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

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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate and well-controlled trials of Monofer in pregnant women. A careful risk/benefit evaluation is therefore 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 many cases be treated with oral iron. Treatment with Monofer should be confined to second and third trimester if the benefit is judged to outweigh the potential risk for both the mother and the foetus. In rare cases, foetal bradycardia has been observed in pregnant women with hypersensitivity reactions (see section 4.8).

Breast-feeding
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.

Fertility
There are no data on the effect of Monofer on human fertility. Fertility was unaffected following Monofer 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

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 foetal bradycardia may occur with parenteral iron preparations.

Flushing in the face, acute chest and/or back pain and tightness sometimes with dyspnea in association with IV 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.

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)**
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
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		Pruritus, urticaria, rash, flushing, sweating, dermatitis	Angioedema
Metabolism and nutritional disorders		Hypophosphataemia	
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	Malaise, influenza like symptoms

Investigations		Hepatic enzyme increased	

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

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via via the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

The iron(III) isomaltoside 1000 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Iron parenteral preparation, ATC code: B03AC

Monofer solution for injection is a colloid with strongly bound 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 andisomaltoside pentamers. 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.

Evidence of a therapeutic response can be seen within a few days of administration of Monofer as an increase in the reticulocyte count. 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.

Clinical efficacy

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

Iron deficiency anaemia outside CKD

The P-Monofer-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 in section 4.2 above 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 ≥2 g/dL 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.(FAS, $p < 0.0001$).

Nephrology

Non-dialysis-dependent chronic kidney disease

The P-Monofer-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 randomized to infusion of 1000 mg single dose or bolus injections of 500 mg.Monofer was both non-inferior to oral iron at week 4 ($p<0.001$) 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).

Haemodialysis-dependent chronic kidney disease

The P-Monofer-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 split doses. Both treatments showed similar efficacy with more than 82% of patients with Hb in the target range (non-inferiority, $p=0.01$).

Oncology

Cancer related anaemia

The P-Monofer-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 over 15 min or bolus injections of 500 mg over 2 min. The primary endpoint was change in Hb concentrations from baseline to week 4. Monofer was non-inferior to oral iron at week

4 ($p<0.001$) and a faster onset of the Hb response was observed with infusion of Monofer.

Gastroenterology

Inflammatory bowel disease

The P-Monofer-IBD-01 trial was an open-label, comparative, randomised, multi-centre, non-inferiority trial conducted in 338 inflammatory bowel disease (IBD) patients 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 over 15 min or bolus injections of 500 mg over 2 min. A modified Ganzoni formula was used to calculate the IV iron need with a target Hb of only 13 g/dL resulting in an average iron dose of 884 mg elemental iron compared to oral iron administered as 200 mg oral iron sulfate once daily for 8 weeks (11,200 mg elemental oral iron in total). The primary endpoint was change in Hb concentrations from baseline to week 8. The patients had mild to moderate disease activity. Non-inferiority in change of Hb to week 8 could not be demonstrated. The dose-response relationship observed with Monofer suggests that the true iron demand of IV iron was underestimated by the modified Ganzoni formula. The Hb response rate was 93% for patients receiving > 1000 mg Monofer.

Women's health

Postpartum

The P-Monofer-PP-01 trial was an open-label, comparative, randomised, single-centre, non-inferiority trial conducted in 200 healthy women with postpartum haemorrhage exceeding 700 mL within 48 hours after delivery. The women were randomised 1:1 to receive either a single dose of 1200 mg Monofer or standard medical care. 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.

5.2 Pharmacokinetic properties

The Monofer formulation contains iron in a strongly bound complex that enables a controlled and 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 1000 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, iron isomaltoside 1000 is rapidly 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 isomaltoside 1000. 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, Monofer 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

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 male reproductive performance and spermatogenic parameters were found at dose level tested.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

6.3. Shelf life

Shelf life of ampoules as packaged for sale
3 years

Shelf life of vials as packaged for sale
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 with sterile 0.9% sodium chloride.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions of the reconstituted and diluted solution see section 6.3.

6.5 Nature and contents of container

Type 1 glass ampoule.

Pack sizes: 5 x 1 ml, 10 x 1 ml, 5 x 2 ml, 10 x 2 ml, 2 x 5 ml, 5 x 5 ml, 2 x 10 ml, 5 x 10 ml

Type 1 glass vial with chlorobutyle rubber stopper and aluminium cap.

Pack sizes: 1 x 1 ml, 5 x 1 ml, 10 x 1 ml, 5 x 2 ml, 10 x 2 ml, 1 x 5 ml, 2 x 5 ml, 5 x 5 ml, 1 x 10 ml, 2 x 10 ml, 5 x 10 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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.

7 MARKETING AUTHORISATION HOLDER

Pharmacosmos A/S

Roervangsvej 30

DK-4300 Holbaek

Denmark

8 MARKETING AUTHORISATION NUMBER(S)

PL 18380/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18/01/2010
Date of latest renewal: 26/11/2014

10 DATE OF REVISION OF THE TEXT

19-05-2017