PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**MONOFERRIC**™

Iron Isomaltoside 1000 for Injection

100 mg elemental iron/mL (as iron isomaltoside 1000)

Solution

Intravenous

Iron, parenteral preparations
ATC B03AC

Manufactured by:
Pharmacosmos A/S
Roervangsvej 30
DK-4300 Holbaek
Denmark

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Imported/Distributed by:
Pfizer Canada Inc.
Kirkland (Québec) H9J 2M5
Canada

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MONOFERRIC™

Iron Isomaltoside 1000 for Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	solution 100 mg/mL elemental iron	None. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

MONOFERRIC™ (Iron Isomaltoside 1000 for Injection) is indicated for the treatment of iron deficiency anemia in adult patients who have intolerance or unresponsiveness to oral iron therapy.

The diagnosis must be based on laboratory tests.

Geriatrics (≥ 65 years of age):
A careful risk benefit assessment is required before MONOFERRIC is used in patients aged > 65 years and close monitoring for adverse events is required (see **WARNINGS AND PRECAUTIONS**, **Special Populations, Geriatrics**).

Pediatrics (< 18 years of age):
MONOFERRIC has not been evaluated in patients less than 18 years of age.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or any of the excipients. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**
- Known serious hypersensitivity to other parenteral iron products
- History of multiple allergies
- Non-iron deficiency anaemia (e.g. hemolytic anaemia)
- Iron overload or disturbances in utilization of iron (e.g. hemochromatosis, hemosiderosis)
- Decompensated liver cirrhosis or active hepatitis

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

MONOFERRIC is contraindicated in patients with any allergy to this drug or known serious hypersensitivity to other parenteral iron products or in patients with any known history of multiple allergies.

The following are clinically significant adverse events:

- Serious hypersensitivity reactions including life threatening and fatal anaphylaxis/anaphylactoid reactions have been reported in patients receiving intravenous iron products including MONOFERRIC (see **Immune, Hypersensitivity** below).
- Serious cases of hypotension (see **Cardiovascular** below).

MONOFERRRIC should only be administered when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions (see **Immune, Hypersensitivity** below).

Patients should be carefully monitored for signs and symptoms of hypersensitivity reactions including monitoring of blood pressure and pulse during and for at least 30 minutes following each administration of MONOFERRIC.

General

Excessive therapy with parenteral iron can lead to excess storage of iron and possible iatrogenic hemosiderosis. Do not administer MONOFERRIC to patients with iron overload (see **CONTRAINDICATIONS**).

Carcinogenesis and Mutagenesis

Carcinogenicity studies have not been conducted. Iron isomaltoside showed no evidence of genotoxicity or mutagenicity in a standard battery of tests. These included an *in vitro* Ames test with and without metabolic activation, an *in vitro* human lymphocyte chromosome aberration test with and without metabolic activation and an in vivo mouse micronucleus test.

Cardiovascular

In clinical studies hypotension was reported in < 1% (16/1640) of patients, including serious events in < 1% (2/1640) of patients who received MONOFERRIC. Hypotension has also been reported in the post-marketing experience. Hypotensive episodes may occur if intravenous injection is administered too rapidly. Observe patients for signs and symptoms of hypersensitivity including hypotension during and for at least 30 minutes following each administration.

Immune

Hypersensitivity: 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. MONOFERRIC is contraindicated in patients with known serious hypersensitivity to other parenteral iron products (see **CONTRAINDICATIONS**).

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).

MONOFERRIC may cause life-threatening and fatal hypersensitivity reactions, including anaphylaxis and/or anaphylactoid reactions. In clinical trials, severe or serious hypersensitivity reactions were reported in 1.04 % (17/1640) of patients who received MONOFERRIC and 0.43 % (7/1640) of these patients reported a severe or serious hypersensitivity reaction within 1 day of dosing. Hypersensitivity reactions have been seen in spontaneously reported adverse events from post-marketing experience (see **ADVERSE REACTIONS**, **Post-market Adverse Drug Reactions**).

MONOFERRIC should only be administered when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitive reactions. Observe patients for signs and symptoms of hypersensitivity during and for at least 30 minutes following each administration of MONOFERRIC. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately.

Infection: There is a risk that iron preparations enhance bacterial growth and inhibit leucocyte function and phagocytosis. Parenteral iron should be used with caution in case of severe acute or chronic infection. In patients with chronic infection a risk/benefit evaluation has to be performed, taking into account the suppression of erythropoiesis. MONOFERRIC should not be used in patients with ongoing bacteraemia.

Sexual Function/Reproduction

Iron isomaltoside 1000 did not affect fertility in male or female rats when administered intravenous (IV) at up to 19 mg/kg/day in males and 32 mg/kg/day in females (3 and 2.5 times the maximum recommended human (2000 mg in a 70 kg human) exposure from a single course of MONOFERRIC). Degenerative changes of the male reproductive system of unknown reversibility were observed in male rats at 80 mg/kg/day thrice weekly (5 times the maximum recommended human exposure from a single course of MONOFERRIC) (see **TOXICOLOGY**).

Skin
MONOFERRIC should be administered with caution to avoid paravenous leakage during administration. Paravenous leakage may lead to irritation of the skin and long lasting brown discoloration at the injection site. In case of paravenous leakage, the administration of MONOFERRIC must be stopped immediately.

Hypophosphataemia
In clinical trials the frequencies of a transient drop in phosphate below 2 mg/dL have been 5-20% in patients treated with MONOFERRIC from the studies in patients with iron deficiency anemia of various aetiologies and 1-2% studies with chronic kidney disease (CKD) patients. Nadir was in the first weeks. No clinical symptoms were reported. One of the risks with profound hypophosphataemia is osteomalacia which has been reported after repeated use of IV iron. No cases of osteomalacia after MONOFERRIC use have been received.

Special Populations

Pregnant Women: There are no studies of MONOFERRIC in pregnant women.

Administration of iron isomaltoside 1000 in pregnant rats at IV doses of 11 and 32 mg Fe/kg/day for 14 days prior to cohabitation and 17 days during gestation (2 and 6 times the maximum recommended human (2000 mg in a 70 kg human) exposure from a single course of MONOFERRIC) resulted in an increase in the incidence of skeletal developmental delays (see **TOXICOLOGY**).

In pregnant rabbits, administration of 43 mg Fe/kg/day iron isomaltoside 1000 for 14 days (7 times the maximum recommended human exposure from a single course of MONOFERRIC) resulted in an increased mortality, abortion, and/or premature delivery, a higher mean litter proportion of postimplantation loss, a corresponding lower mean number and litter proportion of viable fetuses, and lower mean fetal weights. Fetal malformations indicating teratogenicity were noted in the 25 and 43 mg Fe/kg/day groups (4 and 7 times the maximum recommended human exposure from a single course of MONOFERRIC, respectively), and fetal developmental variations were noted in the 43 mg Fe/kg/day (see **TOXICOLOGY**).

Based on findings in nonclinical studies, MONOFFERIC should not be used during pregnancy; if pregnancy occurs, the patients should be informed of the potential risk. MONOFERRIC should not be used in women of childbearing potential not using adequate contraception.

Breast-feeding: Because many drugs are excreted in human milk precaution should be exercised. No formal clinical studies investigating excretion of MONOFERRIC have been performed. A clinical study has shown that maternal milk iron level was higher 3 days after receiving MONOFERRIC compared to those receiving standard medical care (oral iron treatment), however, it had decreased to the same levels as the standard medical care group by week 1 (see **DETAILED PHARMACOLOGY**).

Pediatrics (< 18 years of age): MONOFERRIC has not been evaluated in patients less than 18 years of age.

Geriatrics (> 65): Clinical studies with MONOFERRIC have not identified differences in adverse reactions between elderly and younger adult patients, but there was a higher percentage of patients experiencing serious adverse events (SAEs) and adverse events (AEs) leading to fatal outcome in patients ≥ 65 years (SAEs: < 65 years at 6 %, ≥ 65 years at 19 %; AEs leading to fatal outcome: < 65 years at < 1 %, ≥ 65 years at 3 %). A careful risk benefit assessment is required before MONOFERRIC is used in patients aged > 65 years and close monitoring for adverse events is required.

Hepatic Impairment: MONOFERRIC is contraindicated in patients with decompensated liver cirrhosis or active hepatitis (see **CONTRAINDICATIONS**). 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.

Monitoring and Laboratory Tests

Patients must have confirmed iron deficiency anemia (IDA) based on appropriate laboratory tests before treatment (see **WARNINGS AND PRECAUTIONS**, **General**).

Regularly monitor the haematologic response and iron parameters, such as serum ferritin and transferrin saturation, during parenteral iron therapy. Monitoring of iron parameters such as serum ferritin may assist in recognizing iron accumulation.

Monitor patient's blood pressure and heart rate for signs and symptoms of hypotension before, during and for 30 minutes after each MONOFERRIC administration. Each patient should be observed for adverse effects, including signs and symptoms of hypersensitivity reactions (e.g., urticaria, oedema, bronchospasm, hypotension, cardiorespiratory arrest, syncope, unresponsiveness, or loss of consciousness) during administration and for at least 30 minutes following each MONOFERRIC administration. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Out of 1640 patients treated with MONOFERRIC in phase II and III clinical trials, 869 (53 %) patients reported a total of 2048 treatment-emergent AEs (TEAEs). The most common TEAEs (reported in more than 3 % of patients) by preferred term were headache (52 (3 %)), nasopharyngitis and nausea (45 (3 %) each), vomiting (43 (3 %)), and constipation (41 (3 %)).

Of the 2048 AEs, 193 (9.4 %) TEAEs were serious (SAE). The treatment-emergent SAEs were reported in 153 (9 %) patients. No treatment-emergent SAEs were reported in > 1 % in patients treated with MONOFERRIC. The most common SAE was pneumonia (10 patients) followed by

malignant neoplasm progression (8 patients). A total of 10 SAEs reported in 9 patients (< 1 %) were considered as probably or possibly related to MONOFERRIC. These were anaphylactic reaction, staphylococcal sepsis, angina unstable, grand mal convulsion, dyspnea, rash pruritic, syncope and three cases of hypersensitivity.

Of the 1640 patients treated with MONOFERRIC in clinical trials, 43 (3 %) patients experienced TEAEs leading to withdrawal from study.

Overall in clinical trials, a total of 17/1640 (1.04 %) patients reported a serious or severe hypersensitivity reaction, in which 7 of these cases occurred within 1 day of dosing with MONOFERRIC.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Across the three randomized clinical trials a total of 795 patients received MONOFERRIC. A total of 228 non dialysis dependent patients with CKD (NDD-CKD) were exposed to MONOFERRIC in Study CKD-02. MONOFERRIC was administered either as IV infusions or IV bolus injections. The infusion was given in weekly doses for up to 2 weeks, to a maximum of 1000 mg iron each week until full replacement dose was achieved. The dose was diluted in 100 mL 0.9 % sodium chloride and given over approximately 15-20 minutes. Bolus injections of 500 mg were administered undiluted over approximately 2 minutes, once per week until full replacement dose was achieved. Oral iron was administered as 200 mg iron sulphate daily for 8 weeks. The mean cumulative dose of MONOFERRIC administered to the patients in the infusion and bolus subgroups were 907 ± 170 mg (range: 750:1500 mg) and 926 ± 241 mg (range: 500:2000 mg), respectively. The mean cumulative dose of iron isomaltoside 1000 was 916 ± 208 mg (500:2000 mg).

In Study IDA-01, a total of 333 patients with IDA of various causes other than CKD were exposed to MONOFERRIC, of which, 32 (9.6 %) received a cumulative dose of 1000 mg, 164 (49.2 %) received a cumulative dose of 1500 mg, and 130 (39.0 %) received a cumulative dose of 2000 mg. Seven (2.1 %) patients were listed as receiving 'other' cumulative dose. MONOFERRIC was administered either as an IV infusion of 1000 mg over approximately 15 minutes or as an IV injection of 500 mg over 2 minutes per week, for an individual dose up to a maximum cumulative dose of 2000 mg. A total of 168 patients received 200 mg of IV iron sucrose by infusion up to twice weekly up to a cumulative dose of 2000 mg.

In Study CKD-03, a total of 230 hemodialysis-dependent CKD (DD-CKD) patients were exposed to MONOFERRIC, of which, 114 (50 %) received a dose of 500 mg by IV single bolus injection and 116 (50 %) received a total dose of 500 mg as fractionated (100 mg + 200 mg +

200 mg) IV bolus injections. A total of 117 patients received 500 mg of IV iron sucrose administered as 500 mg fractionated (100 mg + 200 mg + 200 mg) IV bolus injections.

Table 1: Clinical Trial TEAEs Reported in ≥ 1% Patients by Study (Study CKD-02 in patients with NDD-CKD, Study IDA-01 in patients with IDA* and Study CKD-03 in DD-CKD patients)

	CKD-02				CKD-03				IDA-01			
	Iron Isomaltoside 1000		Iron Sulphate Oral		Iron Isomaltoside 1000		Iron Sucrose		Iron Isomaltoside 1000		Iron Sucrose	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Safety Analysis Set	228		117		230		114		333		168	
Any AE(S)	95	(42%)	53	(45%)	110	(48%)	47	(41%)	144	(43%)	65	(39%)
Gastrointestinal Disorders	22	(10%)	15	(13%)	19	(8%)	6	(5%)	47	(14%)	19	(11%)
- Nausea	2	(<1%)	2	(2%)	1	(<1%)			17	(5%)	7	(4%)
- Faeces Discoloured			5	(4%)					2	(<1%)		
- Diarrhoea	7	(3%)	4	(3%)	5	(2%)	2	(2%)	4	(1%)	5	(3%)
- Vomiting	6	(3%)	1	(<1%)	3	(1%)	2	(2%)	7	(2%)	5	(3%)
- Constipation	4	(2%)	2	(2%)	2	(<1%)	1	(<1%)	5	(2%)		
- Abdominal Pain	1	(<1%)							5	(2%)	1	(<1%)
- Dyspepsia	1	(<1%)	1	(<1%)	1	(<1%)			3	(<1%)	2	(1%)
Nervous System Disorders	14	(6%)	6	(5%)	13	(6%)	6	(5%)	30	(9%)	23	(14%)
- Headache	2	(<1%)	2	(2%)	7	(3%)	4	(4%)	18	(5%)	11	(7%)
- Dysgeusia	1	(<1%)							2	(<1%)	5	(3%)
- Dizziness	5	(2%)			1	(<1%)			9	(3%)	4	(2%)
- Paraesthesia	1	(<1%)			3	(1%)			1	(<1%)	1	(<1%)
Infections And Infestations	25	(11%)	12	(10%)	22	(10%)	15	(13%)	24	(7%)	10	(6%)
- Upper Respiratory Tract Infection	1	(<1%)			1	(<1%)	1	(<1%)	4	(1%)	6	(4%)
- Nasopharyngitis	7	(3%)	4	(3%)	6	(3%)	1	(<1%)	3	(<1%)		
- Lower Respiratory Tract Infection	1	(<1%)	1	(<1%)	4	(2%)	3	(3%)				
- Urinary Tract Infection	4	(2%)			1	(<1%)			8	(2%)	1	(<1%)
- Pneumonia	2	(<1%)	2	(2%)	1	(<1%)	1	(<1%)				
Injury, Poisoning And Procedural Complications	2	(<1%)			25	(11%)	9	(8%)	4	(1%)	4	(2%)
- Fall	1	(<1%)			7	(3%)						
- Procedural Hypotension					5	(2%)	1	(<1%)				
- Arteriovenous Fistula Site Complication					2	(<1%)	2	(2%)				
- Procedural Hypertension					3	(1%)						
- Contusion									1	(<1%)	2	(1%)
General Disorders And Administration Site Conditions	23	(10%)	9	(8%)	10	(4%)	5	(4%)	26	(8%)	14	(8%)
- Pyrexia	7	(3%)	4	(3%)	1	(<1%)			6	(2%)		
- Fatigue	3	(1%)							4	(1%)	5	(3%)
- Oedema Peripheral	5	(2%)	2	(2%)					1	(<1%)		
- Chills							2	(2%)	2	(<1%)	1	(<1%)

	CKD-02				CKD-03				IDA-01			
	Iron Isomaltoside 1000		Iron Sulphate Oral		Iron Isomaltoside 1000		Iron Sucrose		Iron Isomaltoside 1000		Iron Sucrose	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
- Device Malfunction							2	(2%)				
- Infusion Site Extravasation											2	(1%)
Skin And Subcutaneous Tissue Disorders	10	(4%)	1	(<1%)	9	(4%)	4	(4%)	31	(9%)	7	(4%)
- Rash	2	(<1%)							14	(4%)	1	(<1%)
- Pruritus	1	(<1%)			3	(1%)	2	(2%)	6	(2%)	1	(<1%)
- Skin Exfoliation									5	(2%)		
- Pruritus Generalised	3	(1%)										
- Hyperhidrosis											2	(1%)
- Skin Discolouration									2	(<1%)	2	(1%)
Musculoskeletal And Connective Tissue Disorders	10	(4%)	3	(3%)	16	(7%)	1	(<1%)	27	(8%)	9	(5%)
- Back Pain	5	(2%)							8	(2%)	2	(1%)
- Pain In Extremity	1	(<1%)	1	(<1%)	5	(2%)			2	(<1%)		
- Arthralgia					4	(2%)			7	(2%)	2	(1%)
- Myalgia									5	(2%)	1	(<1%)
- Muscle Spasms	3	(1%)	1	(<1%)	3	(1%)			4	(1%)	1	(<1%)
- Muscular Weakness	1	(<1%)							2	(<1%)	2	(1%)
Metabolism And Nutrition Disorders	12	(5%)	2	(2%)	8	(3%)	8	(7%)	9	(3%)	2	(1%)
- Hyperphosphataemia	1	(<1%)			5	(2%)	4	(4%)			1	(<1%)
- Hyperkalaemia	6	(3%)			1	(<1%)	1	(<1%)			1	(<1%)
- Hypophosphataemia									6	(2%)		
Investigations	9	(4%)	2	(2%)	11	(5%)	5	(4%)	13	(4%)	7	(4%)
- C-Reactive Protein Increased					6	(3%)	1	(<1%)	4	(1%)	3	(2%)
- Blood Glucose Increased							2	(2%)				
- Electrocardiogram St Segment Depression							2	(2%)				
- Alanine Aminotransferase Increased	1	(<1%)							5	(2%)	2	(1%)
- Aspartate Aminotransferase Increased	1	(<1%)							5	(2%)	2	(1%)
- Blood Calcium Decreased					3	(1%)						
Respiratory, Thoracic And Mediastinal Disorders	4	(2%)	5	(4%)	6	(3%)	2	(2%)	14	(4%)	6	(4%)
- Cough			2	(2%)	2	(<1%)			5	(2%)	1	(<1%)
- Dyspnoea	2	(<1%)	2	(2%)	1	(<1%)	1	(<1%)	5	(2%)	1	(<1%)
- Oropharyngeal Pain			1	(<1%)					5	(2%)		
- Asthma									1	(<1%)	2	(1%)
Vascular Disorders	8	(4%)	4	(3%)	8	(3%)	1	(<1%)	13	(4%)	6	(4%)
- Hypertension	7	(3%)	2	(2%)	3	(1%)	1	(<1%)	5	(2%)	1	(<1%)
- Hypotension	1	(<1%)			3	(1%)			2	(<1%)		

	CKD-02				CKD-03				IDA-01			
	Iron Isomaltoside 1000		Iron Sulphate Oral		Iron Isomaltoside 1000		Iron Sucrose		Iron Isomaltoside 1000		Iron Sucrose	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
- Hot Flush									2	(<1%)	2	(1%)
Blood And Lymphatic System Disorders	2	(<1%)	2	(2%)	2	(<1%)	2	(2%)	1	(<1%)	5	(3%)
- Anaemia	1	(<1%)	2	(2%)	1	(<1%)			1	(<1%)	1	(<1%)
- Neutropenia											2	(1%)
Cardiac Disorders									5	(2%)	2	(1%)
- Palpitations									1	(<1%)	2	(1%)
Reproductive System And Breast Disorders									5	(2%)	3	(2%)
- Menorrhagia									3	(<1%)	2	(1%)

N: Number of Patients
(%): Percentage of Patients

* Causes of IDA included different etiologies: such as abnormal uterine bleeding, gastrointestinal diseases, cancer, bariatric procedures and other conditions leading to significant blood loss.

Hypophosphataemia:

In Study IDA-01, 65 (19.5 %) patients in the MONOFERRIC group and 7 (4.2 %) patients in the iron sucrose group had serum phosphate (*s*-phosphate) level < 2 mg/dL. Hypophosphataemia defined as *s*-phosphate < 2 mg/dL was reported in 3 patients in CKD-02 and 4 patients in CKD-03 (1.3 % and 1.7 % , respectively) in the MONOFERRIC group compared to 1 patient (< 1 %) in the oral iron sulfate group in Study CKD-02 and 2 patients (1.8 %) in the iron sucrose group in Study CKD-03.

One (1) patient treated with MONOFERRIC had *s*-phosphate level < 1 mg/dL (0.8 mg/dL) at week 4 which was normalised (2.6 mg/dL) at the following visit in Study IDA-01. Two patients of the patients in the MONOFERRIC group had *s*-phosphate level < 1 mg/dL in Study CKD-03 and none in Study CKD-02.

Most patients exposed to MONOFERRIC had low *s*-phosphate values for 1-4 weeks and 7 (2.2 %) patients had *s*-phosphate < 2 mg/dL at week 5 in Study IDA-01. In the iron sucrose group, most patients had low *s*-phosphate values for 1-2 weeks and 1 patient had *s*-phosphate < 2 mg/dL at week 5. Thus, the hypophosphataemia events were transient and in most cases normalised at the end of the trial.

No event of hypophosphataemia was considered as an AE in both Study CKD-02 and CKD-03 but was reported as an AE in Study IDA-01 in 6 (2 %) patients.

Post-Market Adverse Drug Reactions

Because these adverse events are spontaneously reported in a voluntary manner from a population of uncertain size, it is not possible to reliably estimate their frequency. The following adverse reactions have been reported from the post-marketing spontaneous reports with MONOFERRIC:

Cardiac disorders:
Bradycardia foetal, cardiac arrest, tachycardia

General disorders and administration site conditions:
Asthenia, chest discomfort, chest pain, chills, feeling abnormal, feeling hot, influenza like illness, infusion site erythema, injection site discolouration, injection site extravasation, pain

Immune:
Hypersensitivity, anaphylactic and anaphylactoid reactions, including very rare cases of anaphylactic shock with a fatal outcome, have been reported

Investigations:
Blood pressure decreased, blood pressure increased, body temperature increased

Musculoskeletal and connective tissue disorders:
Joint swelling, pain in extremity

Nervous system disorders:
Burning sensation, cerebrovascular accident, generalized tonic-clonic seizure, head discomfort, loss of consciousness, paraesthesia, seizure, syncope, tremor

Respiratory, thoracic and mediastinal disorders:
Asphyxia, bronchospasm, pharyngeal edema, respiratory arrest, respiratory distress, wheezing

Skin and subcutaneous tissue disorders:
Angioedema, dermatitis allergic, erythema, generalized erythema, purpura, rash generalized, skin discolouration, swelling face, urticaria

Vascular disorders:
Circulatory collapse, flushing, hypotension, shock

DRUG INTERACTIONS

Overview
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 MONOFERRIC.

Drug-Drug Interactions
Drug interaction studies with MONOFERRIC have not been conducted.

Drug-Food Interactions
Drug-food interaction studies with MONOFERRIC have not been conducted.

Drug-Herb Interactions
Drug-herb interaction studies with MONOFERRIC have not been conducted.

Drug-Laboratory Interactions
Parenteral iron may cause falsely elevated values of serum bilirubin and falsely decreased values of serum calcium.

Large doses of parenteral iron have been reported to give a brown colour to serum from a blood sample drawn four hours after administration.

Drug-Lifestyle Interactions
No studies on the effects on the ability to drive and use machines have been performed.

DOSAGE AND ADMINISTRATION

Dosing Considerations
The dose of MONOFERRIC (Iron Isomaltoside 1000 for Injection) is expressed in terms of mg of elemental iron, with each mL of undiluted MONOFERRIC containing 100 mg of elemental iron.

Recommended Dose and Dosage Adjustment
The iron need and the administration schedule for MONOFERRIC must be individually established for each patient. The optimal haemoglobin (Hb) target level and iron stores may vary in different patient groups and between patients. 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.

The cumulative iron need can be determined using either the Ganzoni formula (1) or the Simplified Table below (2). In the clinical studies with CKD patients, the Ganzoni formula was used and in the clinical study with IDA patients of various causes other than CKD, the Simplified table was used.

1. Ganzoni formula:

Iron need = Body weight$^{(A)}$ x (Target Hb$^{(E)}$ – Actual Hb)$^{(B)}$ x 2.4$^{(C)}$ + depot iron $^{(D)}$
[mg iron] [kg] [g/dL] [mg iron]

(A) It is recommended to use the patient's ideal body weight for obese patients. 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. Consider using a lower haemoglobin target as appropriate based on clinical judgement.

2. Simplified Table:

Iron need

Hb (g/dL)	Patients with bodyweight <70 kg	Patients with body weight ≥70 kg
≥10	1000 mg	1500 mg
<10	1500 mg	2000 mg

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

MONOFERRIC should only be administered when personnel trained to evaluate and manage anaphylactic reactions are immediately available, in an environment where full resuscitation facilities can be assured. Monitor patients carefully for signs and symptoms of hypersensitivity reactions during and following each administration of MONOFERRIC. The patient should be observed for adverse effects for at least 30 minutes following each MONOFERRIC administration (see **WARNINGS AND PRECAUTIONS**, **Immune**, **Hypersensitivity** and **Monitoring and Laboratory Tests**).

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

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

Intravenous bolus injection:
MONOFERRIC may be administered as an intravenous bolus injection up to 500 mg up to once 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 MONOFERRIC 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 20 minutes or more.
Doses exceeding 1000 mg must be administered over 30 minutes or more.
Single doses above 1500 mg are not recommended.

MONOFERRIC must only be diluted in sterile 0.9 % sodium chloride solution. MONOFERRIC should not be diluted to concentrations less than 1 mg iron/mL (not including the volume of the iron isomaltoside 1000 solution) and should be added to maximum 500 mL sterile 0.9 % sodium chloride.

Injection into dialyzer:
MONOFERRIC may be administered during a hemodialysis session directly into the venous limb of the dialyzer under the same procedures as outlined for intravenous bolus injection.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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

Do not administer MONOFERRIC to patients with iron overload. See **CONTRAINDICATIONS**.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Iron is essential to the synthesis of haemoglobin to maintain oxygen transport and to the function and formation of the physiologically important heme and non-heme compounds.

MONOFERRIC (Iron Isomaltoside 1000 for Injection) is a colloid with strongly bound iron in spheroidal iron-carbohydrate particles. The structure of the iron isomaltoside 1000 particle has been characterized by carbon 13 NMR spectroscopic analysis which reveals that the complex forms a stable matrix type structure with about 10 iron (III) atoms to one molecule of isomaltoside pentamer with the iron(III) bound in cavities of the 3-D structure of isomaltoside pentamers, leading to a low content of free iron based on *in vitro* data.

The isomaltoside 1000 component of MONOFERRIC consists of 3-5 glucose units with an average molecular weight of approximately 1000 Da. It has no detectable branching structures as evidenced by careful ^{13}C and ^{1}H NMR spectroscopic analysis. Furthermore isomaltoside 1000 does not contain any reducing sugar residues, which can be involved in complex redox reactions. The MONOFERRIC formulation contains iron in a complex with isomaltoside 1000 that releases bioavailable iron to iron-binding proteins.

Pharmacodynamics

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

Serum ferritin peaks approximately 7 to 9 days after an intravenous dose of MONOFERRIC and slowly returns to baseline after about 3 weeks.

Pharmacokinetics

MONOFERRIC pharmacokinetics was examined across four patient populations. In patients with inflammatory bowel disease, non-haematological malignancies associated with chemotherapy induced anaemia, in stage 5 chronic kidney disease on dialysis therapy and non-dialysis dependent chronic kidney disease. MONOFERRIC pharmacokinetics was examined across a dose range of 100 to 1000 mg. There is no data investigating the pharmacokinetics of single or multiple doses of MONOFERRIC above 1000 mg.

MONOFERRIC demonstrates dose proportional increases up to 500 mg. MONOFERRIC demonstrated linear pharmacokinetics up to 500 mg, with higher doses demonstrating dose dependent pharmacokinetics.

Distribution:
Following intravenous administration of iron complex, it is taken up by the cells in 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 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.

Excretion:
After administration of a single dose of MONOFERRIC 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, MONOFERRIC is not eliminated via the kidneys. Small quantities of iron are eliminated in urine and faeces.

Special Populations

Breast-feeding: In a clinical study in women with post-partum hemorrhage, maternal milk iron levels were measured in a subset of patients. Levels were found to be higher at day 3 in the MONOFERRIC group, decreasing to the same levels as the standard medical care (oral iron treatment) group at week 1 (see **DETAILED PHARMACOLOGY**).

STORAGE AND STABILITY

Store between 15-30 ºC. Do Not Freeze.

For storage conditions of the diluted solution, see below.

MONOFERRIC (Iron Isomaltoside 1000 for Injection) must be only 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 **DOSAGE AND ADMINISTRATION**.

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

Shelf life after first opening (undiluted):

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

Shelf life after dilution with sterile 0.9 % sodium chloride:

From a microbiological point of view, preparations for parenteral administration should be used immediately after dilution with sterile 0.9 % sodium chloride solution.

SPECIAL HANDLING INSTRUCTIONS

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

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

MONOFERRIC (Iron Isomaltoside 1000 for Injection) is a dark brown, non-transparent, sterile aqueous colloidal preservative-free solution. Each mL of MONOFERRIC contains the equivalent of 100 mg of elemental iron in Water for Injection (WFI). Hydrochloric acid and sodium hydroxide may be added to adjust the pH.

MONOFERRIC is available in glass single use vials.

MONOFERRIC is available in the following formats:

Single dose vial size	Number of vials per box
1 mL	5
5 mL	1 or 5
10 mL	1 or 2

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Iron isomaltoside 1000

Chemical name: Iron (III) hydroxide isomaltoside 1000
α-D-Glucan, (1-6)-, reduced, reaction products with iron oxyhydroxide ($Fe(OH)_3$)

The drug substance is a colloidal particle containing approximately 640 repeat units of the following molecular formula. The formula is normalized with respect to iron stoichiometry.

Molecular formula: $\{FeO_{(1-3X)}\,(OH)_{(1+3X)}\,(C_6H_5O_7^{3-})_X\}$, $(H_20)_T$, - $(C_6H_{10}O_6)_R(-C_6H_{10}O_5-)_Z(C_6H_{13}O_5)_R$, $(NaCl)_Y$

X= 0.0311; T = 0.25; R = 0.14; Z = 0.49; Y = 0.14

Molecular mass: 235 g/mol
The apparent molecular weight = 150kDa

Structural formula: Iron Isomaltoside 1000 has a matrix structure with the overall molecular formula as described above. The exact structure of the matrix has not been unambiguously determined.

Physicochemical properties: MONOFERRIC is a sterile colloidal solution containing a complex of iron (III) with isomaltosides of an average molecular weight of approximately 1000 Daltons. The pH is between 5.0 and 7.0.

CLINICAL TRIALS

The 3 Phase III trials included a study in iron deficiency anemia from different etiologies (IDA-01), including gastroenterology, gynecology, oncology and unknown or unspecified IDA, a study conducted in non-dialysis dependent CKD patients (CKD-02), and a study conducted in hemodialysis dialysis dependent CKD patients (CKD-03).

Iron Deficiency Anemia – Study IDA-01

<table>
<tr><td>Trial Design</td><td>Phase III, 2:1 randomised, open-label, comparative, non-inferiority study</td></tr>
<tr><td>Diagnosis</td><td>• IDA of different etiologies, including gastroenterology, gynecology, oncology and unknown or unspecified IDA
• Hb < 11 g/dL. TSAT < 20 %, ferritin < 100 ng/mL
• Not receiving erythropoiesis stimulating agent (ESA) treatment</td></tr>
<tr><td>Dosage, route of administration, duration</td><td>MONOFERRIC IV infusion of 1000 mg over approximately 15 minutes or IV bolus injection of maximum 500 mg over 2 minutes in an individual dose. Additional doses separated by 1 week. Hb and body weight used to calculate cumulative dose. The simplified table below was used to calculate the full iron replacement dose.
<table>
<tr><th>Hb (g/dL)</th><th colspan="2">Cumulative Dose</th></tr>
<tr><th></th><th>BW < 70 kg</th><th>BW ≥ 70 kg</th></tr>
<tr><td>≥ 10</td><td>1000 mg</td><td>1500 mg</td></tr>
<tr><td>< 10</td><td>1500 mg</td><td>2000 mg</td></tr>
</table>
Iron sucrose infusion of 200 mg over approximately 30 minutes up to twice weekly up to max cumulative dose of 2000 mg. The Ganzoni formula was used to calculate full iron replacement dose.
Duration – 5 weeks

The mean (SD) cumulative dose of MONOFERRIC was 1640.2 (357.6) mg and of iron sucrose 1127.9 (343.3) mg. A total of 32 (9.6 %) patients received a cumulative dose of 1000 mg MONOFERRIC, 164 (49.2 %) patients received 1500 mg, 130 (39.0 %) patients received 2000 mg, and 7 (2.1 %) patients received other dosages.</td></tr>
<tr><td>Study patients (n)</td><td>491 (Full Analysis Set (FAS))</td></tr>
</table>

Table 2 Baseline Demographics and Laboratory Values – IDA-01

	MONOFERRIC (n=330)	Iron Sucrose (n=161)
Mean Age, years (±SD) Range	49.2 (15.7) 19; 95	46.8 (15.1) 19; 87
Gender (M/F %)	10/90	9/91
Ethnic Origin (%) Caucasian Black Asian Other	 62 34 1 3	 62 33 1 4
Mean Hb, g/dL (±SD)	9.39 (1.15)	9.39 (1.31)
Mean s-ferritin, ng/L (±SD)	14.3 (32.8)	15.6 (47.2)
Mean TSAT, % (±SD)	5.8 (5.0)	6.4 (5.9)
Type of disease causing IDA (N, %) Gastroenterology Gynaecology Oncology Others	 111 (33.6) 158 (47.9) 6 (1.8) 55 (16.7)	 53 (32.9) 79 (49.1) 3 (1.9) 26 (16.1)

The primary endpoint analysis (proportion of patients with an Hb increase of ≥ 2 g/dL from baseline at any time from week 1 to week 5) showed that there were more responders in the MONOFERRIC group compared with the iron sucrose group, with a risk difference of 16.7 %-points in the FAS and 15.9%-points in the PP set. Since the lower end of the 95 % CI for the risk difference was above 12.5%-points in both the FAS and PP analysis set, non-inferiority of MONOFERRIC to iron sucrose could be claimed. As non-inferiority was proven, the predetermined test for superiority was performed, which also confirmed superiority of MONOFERRIC compared with iron sucrose (p<0.0001, Table 3).

Table 3 Results for the Primary Endpoint and Clinically Relevant Secondary Endpoints – IDA-01

	MONOFERRIC	Iron Sucrose
Primary Endpoint		
Proportion of patients with an Hb increase of ≥ 2 g/dL from baseline at any time from week 1 to week 5		
FAS (n, %)	330 (100.0)	161 (100.0)
Responders, n (%)	226 (68.5)	83 (51.6)
Risk Difference (%) [95 % CI]	16.7 [7.5; 25.7]	
Superiority test, p-value(1)	<0.0001	
Secondary Endpoints:		
Time (days) to Hb increase ≥ 2 g/dL (FAS)		
Median	26	37
HR [95%CI]	2.488 [1.916; 3.230]	
p-value	<0.0001	
Change in Hb (g/dL) from baseline to week 5 (FAS)		
Mean (±SD)	2.52 (1.41)	2.05 (1.27)
Estimate Difference	0.46 [0.30; 0.62]	
p-value	< 0.0001	
Change in *s*-ferritin (ng/mL) from baseline to week 5 (with outlier excluded)(FAS)[2]		
Mean (±SD)	241.2 (209.3)	185.7 (166.8)
Estimate Difference	58.8 [21.8; 95.8]	
p-value	0.0019	
Change in TSAT(%) from baseline to week 5 (FAS)		
Mean (±SD)	15.6 (8.6)	11.8 (9.5)
Estimate Difference	3.50 [1.89; 5.10]	
p-value	< 0.0001	

CI, confidence interval; FAS, full analysis set; %, percentage of patients. Risk difference adjusted for strata using the Cochran-Mantel-Haenszel method. *P*-value from a Cochran-Mantel-Haenszel Chi-square test adjusted for strata.
Non-inferiority can be claimed if the lower bound of the 95 % CI is above -0.125.
[1]Similar results was obtained in the per protocol (PP) analysis set (*p*=0.0002).
[2]One patient had s-ferritin value at week 2 of > 100000 ng/mL (outlier) and a sensitivity analysis was performed excluding this value.

Iron Deficiency Anemia in Non-dialysis-dependent Chronic Kidney Disease (NDD-CKD) Patients - Study CKD-02

Trial Design	Phase III, 2:1 randomised, comparative, open-label, non-inferiority study
Diagnosis	NDD-CKD, Hb < 11 g/dL, TSAT < 20 %, ferritin < 200 ng/mL Not receiving ESA treatment Excluding patients with known intolerance to oral iron therapy.
Dosage, route of administration, duration	Iron need was calculated according to Ganzoni formula*. Patients treated with MONOFERRIC either received IV infusion (group A1) of maximum 1000 mg MONOFERRIC as single doses over 15 minutes; full iron replacement achieved by 1 or up to 2 doses at a weekly interval or IV bolus injections (group A2) of 500 mg MONOFERRIC administered over 2 minutes once weekly until full replacement dose was achieved. The maximum dosage per infusion was 1000 mg for patients with a weight > 45 kg, 750 mg for patients with a weight between 35.1 and 45 kg, and 500 mg for patients with a weight of 30-35 kg. The maximum dose per bolus injection was 500 mg. Patients who received iron sulphate (group B) were treated daily for 8 weeks with 200 mg.
Study patients (n)	351

*Ganzoni formula:

Iron need = Body weight$^{(A)}$ x (Target Hb$^{(E)}$ – Actual Hb)$^{(B)}$ x 2.4$^{(C)}$ + depot iron $^{(D)}$

[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 13 g/dL in the Ganzoni formula.

Table 4 Baseline Demographics and Laboratory Values – CKD-02

	MONOFERRIC (n=233)	**Iron Sulphate (n=118)**
Mean Age, years (±SD) Range	58 (15.54) 22; 93	58 (16.34) 20; 90
Gender (M/F %)	39/61	54/46
Ethnic Origin (%) Caucasian Black Asian Other	 37 - 60 3	 40 1 54 5
Mean Hb, g/dL (±SD)	9.67 (1.13)	9.64 (1.05)
Mean s-ferritin, µg/L (±SD)	94.99 (112.79)	98.81 (90.19)
Mean TSAT, % (±SD)	18.10 (27.45)	15.51 (7.76)

The primary endpoint analysis (change in Hb from baseline to week 4) showed that MONOFERRIC was non-inferior to iron sulphate in its ability to increase Hb from baseline to week 4 in both the FAS and PP data sets (p<0.0001). The non-inferiority margin was set as -0.5 g/dL. As non-inferiority was proven and the 95 % CI lay entirely above 0, the predetermined test for superiority was performed. MONOFERRIC showed a significantly higher increase in Hb concentration from baseline to week 4 compared to iron sulfate (FAS: p=0.039; PP: p=0.047; Table 5).

Table 5 Results for the Primary Endpoint and Clinically Relevant Secondary Endpoints - CKD-02

	MONOFERRIC	Iron Sulfate
Primary Endpoint		
Change in Hb (g/dL) from baseline to week 4 (FAS)		
Mean (±SD)	0.57 (0.94)	0.35 (0.96)
Difference estimate [95% CI]	0.2216 [0.012: 0.431]	
Non-inferiority p-value[(1)]	<0.0001	
Testing of superiority p-value[(2,3)]	0.0385	
Secondary Endpoints		
Number of patients who had a change in Hb concentration ≥ 1.0 g/dL from baseline to week 4 (FAS)		
n (%)	62 (29.7)	28 (25.9)
p-value[(4)]	0.3944	
Change in Hb (g/dL) from baseline to week 8 (FAS)		
Mean (±SD) g/dL	0.92 (1.19)	0.45 (1.04)
Difference estimate [95% CI]	0.4450 [0.199: 0.691]	
p-value[(2,3)]	0.0004	
Change in concentrations of *s*-ferritin (µmol/L) from baseline to week 4 (FAS)		
Mean (±SD)	280.96 (175.51)	58.44 (337.50)
Difference estimate [95% CI]	235.2231 [169.697: 300.749]	
p-value[(2,3)]	< 0.0001	
Change in TSAT (%) from baseline to week 4 (FAS)		
Mean (±SD)	6.99 (29.40)	4.97 (8.87)
Difference estimate [95% CI]	4.7666 [2.452: 7.082]	
p-value[(2,3)]	< 0.0001	

[1] Non-inferiority was tested by shifting the distribution of difference estimate by a non-inferiority margin -0.5 and testing the equality between treatment groups by deriving p-value. Similar result was obtained in the PP analysis set (p<0.0001).
[2] P-value for infusion, bolus MONOFERRIC group indicates the significance of treatment differences.
[3] MMRM included treatment, country and stratum (past treatment with parenteral iron (Yes/No) and current eGFR be-tween 15-45 mL/min or between 46-59 mL/min) as factors and baseline value as covariates using PROC Mixed procedure of SAS software.
[4] P-value was calculated by logistic regression with treatment and stratum as factors and baseline values as covariates using PROC LOGISTIC procedure of SAS.

Iron Deficiency Anemia in Hemodialysis-dependent Chronic Kidney Disease Patients - Study CKD-03

Trial Design	Phase III, 2:1 randomised, comparative, open-label, non-inferiority study
Diagnosis	CKD-5D in haemodialysis Hb between 9.5 and 12.5 g/dL (both values included), TSAT < 35 %, ferritin < 800 ng/mL Patients receiving ESA treatment were in stable dosing
Dosage, route of administration, duration	All patients received a cumulative dose of 500 mg iron. Treatment Groups: A. MONOFERRIC: administered as a single intravenous bolus injection of 500 mg over 2 minutes at baseline or administered in 500 mg fractionated doses of 100 mg at baseline and 200 mg each at weeks 2 and 4 as intravenous bolus injections over 2 minutes. B. Iron sucrose: administered as 500 mg fractionated doses of 100 mg at baseline and 200 mg each at weeks 2 and 4 as intravenous bolus injections
Study patients (n)	351

Table 6 Baseline Demographics and Laboratory Values – CKD-03

	MONOFERRIC N= 234	**Iron Sucrose N=117**
Mean Age, years (±SD) Range	60.13 (16.21) 18; 89	59.50 (15.39) 26; 84
Gender (M/F %)	68/32	63/37
Ethnic Origin (%)		
Caucasian:	66	63
Black	6	4
Asian	27	32
Other	1	1
Mean Hb, g/dL (±SD)	11.20 (0.83)	11.08 (0.93)
Mean s-ferritin, µg/L (±SD)	350.88 (186.17)	357.74 (192.98)
Mean TSAT, % (±SD)	22.20 (17.90)	22.57 (8.49)

The primary endpoint analysis (ability to maintain Hb between 9.5 and 12.5 g/dL) showed that the majority (> 82 %) of patients treated with either MONOFERRIC or iron sucrose were able to maintain Hb between 9.5 and 12.5 g/dL at week 6. The test for non-inferiority showed that iron isomaltoside 1000 was non-inferior to iron sucrose (FAS: p=0.0106; PP: p=0.0057) (Table 7). An analysis has been performed with a more narrow Hb range of 10-12 g/dL. The proportion of responders was 63 % and 64 % in patients treated with MONOFERRIC or iron sucrose, respectively, with no statistically significant difference between the groups. Thus, this analysis shows similar response as the primary endpoint analysis.

Table 7 Results for the Primary Endpoint and Clinically Relevant Secondary Endpoints - CKD-03

	MONOFERRIC	Iron Sucrose
Primary Endpoint		
Proportion of patients who were able to maintain Hb between 9.5 and 12.5 g/dL (both values included) at week 6 (FAS)		
FAS (n, %)	226	115
Maintained	187 (82.7)	95 (82.6)
Not maintained	39 (17.3)	20 (17.4)
Risk difference [95% CI]	1.0 [-7.4:9.4]	
Non-inferiority *p*-value[(1)]	0.0106	
Secondary Endpoints:		
Change in *s*-ferritin (µg/L) from Baseline to week 4 (FAS)		
Mean (±SD)	128.04 (157.75)	86.33 (126.79)
Difference estimate [95% CI]	49.3393 [18.174:80.505]	
p-value[(2)]	0.0020	
Change in TSAT (%) from Baseline to week 4 (FAS)		
Mean (±SD)	1.80 (19.26)	2.85 (8.98)
Difference estimate [95% CI]	-0.9972 [-3.090:1.095]	
p-value[(2)]	0.3487	
Change in Reticulocytes from Baseline to week 1 (FAS)		
Mean (±SD)	0.12 (0.42)	-0.02 (0.38)
Difference estimate [95% CI]	0.1540 [0.066:0.242]	
p-value[(2)]	0.0006	

[1]Adjusted risk difference, 95 % CI and p-value were calculated for treatment differences (MONOFERRIC - iron sucrose) using generalised linear model using the identity link function with treatment and stratum (s-ferritin (< 100 versus ≥ 100 ng/mL)) as factors and baseline value as covariate using PROC GENMOD procedure of SAS software. Similar results was obtained in the PP analysis set (p=0.0057).

[2]MMRM included treatment, visit, treatment*visit interactions, country and stratum (*s*-ferritin [< 100 versus ≥ 100 ng/mL]) as factors and baseline values as covariates using PROC Mixed procedure of SAS software.

DETAILED PHARMACOLOGY

The efficacy of a single dose of iron oligosaccharide (similar to iron isomaltoside 1000 for the purpose of non-clinical evaluations) was demonstrated in male and female 4 week-old iron deficient piglets. Hematological parameters normalized one week after subcutaneous administration of iron oligosaccharide at a dose of 50 mg Fe/kg. In addition, no treatment-related adverse clinical signs were observed during the study period.

Intravenous doses of 5, 20 and 80 mg of iron (III)-hydroxide oligosaccharide (similar to iron isomaltoside 1000 for the purpose of non-clinical evaluations)/kg produced no behavioral or physiological changes in mice and no marked or statistically significant effects on spontaneous locomotor activity or hexobarbital-induced sleeping times. Additionally, ataxia was not induced, nor were any notable anticonvulsant or proconvulsant effects; the pain response was not influenced. There was no effect on gastrointestinal motility in mice, and concentrations up to 500 µg Fe/mL produced no marked contractions in the isolated guinea pig ileum. In addition, intravenous administration of 5 and 20 mg Fe/kg in dogs produced no effects on any of the measured hemodynamic parameters, contractile and electrical status of the myocardium, status

and resistance of the peripheral vasculature, or any of the respiratory status parameters when compared to vehicle administration. Intravenous administration of 5 and 20 mg Fe/kg in dogs also produced no marked or statistically significant changes in body temperature when compared with the vehicle-treated animals.

A significant decrease in urinary output for 2-5 hours post dose was seen in Wistar rats at 80 mg Fe/kg when iron(III)-hydroxide oligosaccharide was administered as a single intravenous injection. Additionally, there was a statistically significant decrease in urinary sodium ion excretion and a significant increase in urinary total protein.

Human Pharmacokinetics

Six clinical PK trials have been carried out with different dosages (100, 200, 250, 500, 1000 mg) of MONOFERRIC in patients with inflammatory bowel disease (IBD), non-haematological malignancies associated with chemotherapy induced anemia (CIA), in stage 5 chronic kidney disease on dialysis therapy and non-dialysis dependent chronic kidney disease (CKD). There seems to be a dose-dependent increase in AUC and C_{max} which is observed within all 3 patient populations; IBD, CKD, and CIA. $T_{½}$ varies between 23.2 to 87.9 h with the highest value observed for patients dosed with 1000 mg of MONOFERRIC. Studies are further described below.

In one cross-over study, 12 adults with IBD (7 females /5 males) received bolus injections of either 100 and 200 mg or 200 and 100 mg of MONOFERRIC with at least 4 weeks between doses. A dose dependent increase in exposure of free and bound iron was observed. Elimination rates were found to be similar for both doses for each the free and bound iron. The fraction bound/free iron decreases significantly during the 72 hour observation period and is dependent on dose however the decrease shows the same rate for both dose levels. Approximately 1 % of the infused total dose of MONOFERRIC and an insignificant amount (0.04 – 0.07%) of the free iron was excreted in the urine.

In 16 adults with IBD (8 males/8 females) treated with escalating doses (500 mg IV bolus or 1000 mg infusion) of MONOFERRIC, statistically significant dose-dependent increase was observed in AUC (p=0.0212) and C_{max} (p=0.0030), and a statistically significant dose-dependent decrease in K_e (p=0.0116). There was a dose-dependent increase in AUC_{0-t} and $T_{1/2}$ but the difference was not statistically significant.

In 18 adults with CKD stage 5D (12 male/6 female), randomized to receive either 100 mg, 200 mg or 500 mg of MONOFERRIC by IV bolus, an increase in PK levels of total s-iron with escalating doses was demonstrated from the time of administration to 7 days post-dose. The PK data showed a dose-dependent increase in AUC, AUC_{0-t}, and C_{max} with no difference in K_e and $T_{½}$ between the 100, 200, and 500 mg IV bolus dose of MONOFERRIC. The $T_{½}$ was between 28.86 and 31.14 hours and T_{max} was between 0.57 and 1 hour.

Sixteen adults with NDD-CKD (11 males, 5 females) were treated with either a 500 mg IV bolus or 1000 mg IV infusion of MONOFERRIC. A numerical but not statistically significant higher AUC (p = 0.0559), T_{max} (p = 0.2703), and $T_{½}$ (p = 0.0859) was observed in the 1000 mg IV

infusion group compared to the 500 mg IV bolus group. There was a statistically significant dose-dependent increase in AUC_{0-t} ($p < 0.0001$) and a statistically significant dose-dependent decrease in K_e ($p = 0.0062$). The $T_{½}$ was between 39.87 and 87.87 hours and the T_{max} was between 1.13 and 1.53 hours.

A study in 16 adults with chemotherapy induced anemia non-hematological malignancies (3 males/ 13 females), patients were administered MONOFERRIC by either a 500 mg intravenous bolus injection or 1000 mg intravenous infusion. A dose-dependent increase was observed in AUC, AUC_{0-t}, C_{max}, T_{max}, and $T_{½}$, and a marginal decrease was observed with increasing doses in Ke. The $T_{½}$ was between 37.5 and 47 hours and the T_{max} was between 1.04 and 1.07 hours.

MONOFERRIC was administered to patients (6 males/ 5 females) with non-hematological malignancies associated with chemotherapy induced anemia by either 250 mg IV bolus injection or 500 mg intravenous infusion. A numerical but not statistically significant higher AUC and AUC_{0-t} was observed in the 500 mg IV infusion group compared to the 250 mg IV bolus group. There was a statistically significant dose-dependent increase in C_{max} ($p = 0.0142$) between the treatment groups. $T_{½}$, T_{max}, and K_e were comparable between the treatment groups and no statistically significant differences were observed between the treatment groups. The $T_{½}$ was between 33 and 42.49 hours and the T_{max} was between 0.76 and 1.37 hours.

Excretion in milk
In a subset of patients (n=65) in a post-partum hemorrhage study, the mean maternal milk iron level was higher in the MONOFERRIC group (72.1 µg/dL) than in the standard medical care (oral iron treatment) group (40.0 µg/dL) at day 3. However, at week 1 the mean maternal milk iron level in the MONOFERRIC group had decreased to the same level as in the standard medical care group (46.8 µg/dL and 44.2 µg/dL, respectively).

A total of 8 patients in the MONOFERRIC group had an abnormally high maternal milk iron level (i.e. > 80 µg/dL) at day 3 (81-164.4 µg/dL) compared to 1 patient in the standard medical care group (99.4 µg/dL). At week 1, the corresponding numbers were 1 patient in the MONOFERRIC group (99.8 µg/dL) and 2 patients in the standard medical care group (115.4 µg/dL).

TOXICOLOGY

Single-Dose Toxicity
In single-dose intravenous toxicity studies, the minimum lethal dose in male mice was 125 mg Fe/kg (HED =10 mg/kg, the maximum recommended weekly clinical dose is 20 mg/kg), and the no observed adverse effects level (NOAEL) was determined to be 80 mg Fe/kg in male and female mice corresponding to a HED of 6.5 mg/kg.

In male and female rats, iron isomaltoside administered at 80 mg/kg produced a decrease in urinary output, a decrease in urinary Na^+ output and an increase in protein excretion. No signs of toxicity were observed at doses up to 250 mg Fe/kg (HED= 42 mg/kg). Treatment related clinical signs of reddish brown urine, swollen dark feet, swollen face and muzzle, dark colored skin, dark

colored mouth and rough coat were observed at single doses of 500 and 1000 mg Fe/kg between days 0-4. No adverse histopathological changes were observed in the kidneys, liver, and heart of rats receiving 142 mg Fe/kg, but accumulation of iron pigment was noted in tubular epithelial cells and in interstitial macrophages in the kidneys, and in macrophages of medullary sinuses of the lymph nodes. The acute intravenous approximate lethal dose in rats was determined to be > 1000 mg/kg (HED of > 169 mg/kg).

Repeat Dose Toxicity

Repeat-dose toxicity studies were conducted in rats and beagle dogs for a duration of up to 4 weeks.

In a dose-range finding study, male rats were administered doses up to 250 mg Fe/kg, once on days 0, 2, 5, 7, and 9. In the main definitive study, male and female rats received up to 80 mg Fe/kg, 3 times per week for 4 weeks.

In rats, general signs of systemic toxicity (body weight loss) were evident at all dose levels except for effects on the male reproductive system. Degeneration of the seminiferous epithelium, degenerate germ cells in the epididymides, and atrophy of the prostate were only observed in the 80 mg Fe/kg dose group (HED=14 mg/kg) of the 4-week toxicity study. Due to the lack of a recovery group in this study, it is not known whether these degenerative changes are reversible following a non-dosing period.

Beagle dogs were administered doses up to 80 mg Fe/kg (HED=43 mg/kg), 3 times per week for 4 weeks. No toxicologically relevant clinical signs of toxicity were seen in dogs administered 5, 20, and 80 mg/kg 3 times a week for 4 weeks. In the dose tolerance study where dogs received 50 mg Fe/kg on days 0, 2, 5, 7, 9 and 12, clinical signs of toxicity were seen in dogs on Day 9 at cumulative doses over 250 mg/kg.

In the dose range-finding study, dose-dependent body weight losses/decreases in body weight gains were observed in rats, although body weight gains recovered during the 7-day post-treatment period. No treatment-related effects on mean body weights were observed in dogs. In both species, a dose-dependent increase in tissue discoloration was noted at macroscopic and microscopic examinations and hyperplasia and brown pigment in macrophages were seen in the Kuppfer cells in all treated groups. Increases in the liver weights were seen in both species at 80 mg Fe/kg.

In laboratory investigations, a statistically significant increase in the levels of alanine aminotransferase, aspartate aminotransferase, cholesterol, and globulin, and a decrease in the albumin to globulin (A/G) ratio were seen in male rats, and a statistically significant increase in the levels of alanine aminotransferase, alkaline phosphatase, cholesterol, total protein, urea nitrogen, and globulin, and a decrease in the A/G ratio were seen in female rats. Similarly, in dogs, alkaline phosphatase, aspartate aminotransferase, γ-glutamyl-transferase, and triglycerides were elevated in males at 80 mg Fe/kg, while albumin was decreased in females at 80 mg Fe/kg.

Mutagenicity and Genotoxicity
No evidence of mutagenic activity was found in an *in vitro* bacterial reverse mutation assay, an *in vitro* chromosomal aberrations test and an *in vivo* mouse micronucleus assay.

Carcinogenicity
Carcinogenicity studies have not been conducted.

Reproductive and Developmental Toxicity
In a fertility and embryo-fetal development study in rats, iron isomaltoside 1000 had no effect on male or female fertility or general reproductive functions in rats at doses up to 19 mg Fe/kg/day (3 times the maximum recommended human (2000 mg in a 70 Kg human)) exposure from a single course of MONOFERRIC) in males administered for 28 days prior to mating and up to 32 mg Fe/kg/day (2.5 times the maximum recommended human exposure from a single course of MONOFERRIC) in females dosed for 14 days prior to mating. Dosing through gestation Day 17 in pregnant rats resulted in a significant increase in the incidence of skeletal developmental delays (bent scapula and/or bent rib(s)) at 11 and 32 mg Fe/kg/day (2 and 6 times the maximum recommended human exposure from a single course of MONOFERRIC).

In a repeat-dose toxicity study in rats given iron isomaltoside 1000 at an intravenous dose of 80 mg Fe/kg (5 times the maximum recommended human exposure from a single course of MONOFERRIC), 3 times per week for 4 weeks, degeneration of the seminiferous epithelium, degenerate germ cells in the epididymides, and atrophy of the prostate were observed. Due to the lack of a recovery group in this study, it is not known whether these degenerative changes are reversible following a non-dosing period.

Administration of iron isomaltoside 1000 to pregnant rabbits did not result in maternal effects at doses of 11 and 25 mg Fe/kg/day for 14 days. Maternal toxicity was limited to the 43 mg Fe/kg/day dose group (7 times the maximum recommended human exposure from a single course of MONOFERRIC, respectively), as evidenced by increased mortality, abortion, and/or premature delivery for several females at this dose group. The 43 mg Fe/kg/day dose group was associated with a higher mean litter proportion of post-implantation loss, a corresponding lower mean number and litter proportion of viable fetuses, and lower mean fetal weights. Intrauterine growth, survival, external, visceral and skeletal fetal morphology were unaffected at 11 mg Fe/kg/day the pregnant rabbits given iron isomaltoside 1000. Fetal malformations (domed head, narrow pectoral region, carpal and/or tarsal flexure, cleft palate, microglossia, narrow pelvic region, high-arched palate, hydrocephaly, small brain and absent cartilaginous bands on the trachea) were noted in the 25 and 43 mg Fe/kg/day groups (4 and 7 times the maximum recommended human exposure from a single course of MONOFERRIC, respectively), and fetal developmental variations were noted at 43 mg Fe/kg/day.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

PrMONOFERRIC™
Iron Isomaltoside 1000 for Injection

Read this carefully before you start taking **MONOFERRIC** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **MONOFERRIC**.

Serious Warnings and Precautions

MONOFERRIC should not be used in patients allergic to this drug or other injectable iron products.

MONOFERRIC should not be used in patients with any known history of multiple allergies.

MONOFERRIC can cause severe side effects, such as:
- Allergic reactions causing death (anaphylaxis)
- Serious cases of low blood pressure (hypotension)

Only use MONOFERRIC if personnel are able to treat severe allergic reactions without delay. You will be monitored for signs and symptoms of an allergic reaction for at least 30 minutes after treatment with MONOFERRIC.

What is MONOFERRIC used for?
MONOFERRIC is used to raise your level of iron (sometimes called 'iron deficiency anaemia') when:
- You cannot tolerate oral iron or
- Oral iron therapies do not work for you

How does MONOFERRIC work?
MONOFERRIC is used to replenish your body's iron stores. Iron is needed to make haemoglobin, which allows red blood cells to carry oxygen throughout your body.

What are the ingredients in MONOFERRIC?
Medicinal ingredient: iron isomaltoside 1000
Non-medicinal ingredients: hydrochloric acid, sodium hydroxide, water for injection

MONOFERRIC comes in the following dosage forms:
100 mg elemental iron/mL

Do not use MONOFERRIC if:
- You are allergic to this drug or any of the ingredients
- You have a history of serious allergies to other injectable iron medications

- You have a history of multiple types of allergies
- You have anemia **not** caused by iron deficiency (hemolytic anaemia)
- You have too much iron (iron overload) or a problem in the way your body uses iron (hemochromatosis, hemosiderosis)
- You have liver problems (cirrhosis, hepatitis)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MONOFERRIC. Talk about any health conditions or problems you may have, including if you:

- Have a history of drug allergies
- Have lupus (an immune system disease where the body's own defence system attacks normal tissue)
- Have rheumatoid arthritis (joint swelling)
- Have severe asthma, eczema (itchy, red skin) or other allergies
- Have low blood pressure (hypotension)
- Have a severe infection
- Are pregnant or planning to become pregnant
- Are breastfeeding or planning to breastfeed
- Are older than 65 years of age

Other warnings you should know about:

- Incorrect administration of MONOFERRIC may cause leakage of the product at the injection site. This may lead to irritation of the skin and possibly long lasting brown discoloration at the site of injection. Tell your doctor or nurse immediately if you notice any leakage. They will need to stop the administration.
- Do not become pregnant while taking MONOFERRIC as it may harm your unborn child. Use effective methods of birth control while taking MONOFERRIC. If you do become pregnant while taking MONOFERRIC, tell your doctor right away.
- MONOFERRIC may pass into breast milk. Do not breastfeed while you are taking MONOFERRIC. If you are planning to breastfeed, tell your doctor.

Give yourself time after taking MONOFERRIC to see how you feel before driving a vehicle or using machinery.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with MONOFERRIC:

- MONOFERRIC can reduce the effect of oral iron.

How to take MONOFERRIC:

Your doctor will calculate how much MONOFERRIC you will be given. The dose will be based on your weight and iron need.

Your doctor or nurse will give MONOFERRIC in one of the following ways:

- an injection in your vein of up to 500 mg of iron (over approximately 2 minutes) up to once a week
- an infusion in your vein of up to 1500 mg of iron (over approximately 20-30 minutes), once a week
- directly into the dialyzer during a hemodialysis session

MONOFERRIC will be given in a location where any allergic events can be treated immediately.

You will be carefully observed during MONOFERRIC treatment and for at least 30 minutes after by your doctor or nurse. If you have any of the following symptoms of an allergic reaction or begin to feel unwell while receiving MONOFERRIC, tell your doctor or nurse right away:

- Dizzy or light-headed
- Swelling of your face, tongue or throat
- Difficulty swallowing
- Itching, rash or hives
- Difficulty breathing
- Nausea or abdominal pain

Overdose:

If you think you have taken too much MONOFERRIC, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

What are possible side effects from using MONOFERRIC?
These are not all the possible side effects you may feel when taking MONOFERRIC. If you experience any side effects not listed here, contact your healthcare professional.

Side effects of MONOFERRIC may include the following:

- abdominal pain
- back pain
- constipation
- cough
- difficulty breathing (dyspnoea)
- dizziness
- fatigue
- headache
- indigestion (dyspepsia)
- joint pain
- muscle pain
- muscle spasms
- muscle weakness
- nausea
- rash

- skin exfoliation
- itchy skin (pruritus)
- skin discolouration
- sore throat
- inflammation of nose and throat (nasopharyngitis)
- pneumonia
- swelling of hands and feet (peripheral edema)
- taste disturbance (dysgeusia)
- tingling sensation (paraesthesia)
- urinary tract infection

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON			
Allergic Reaction (hypersensitivity reaction**)**: possibly life threatening dizziness, severe itching, hives, nausea, difficulty breathing, rash, low blood pressure		√	√
Malignant neoplasm progression (an existing tumor gets worse)		√	
Pneumonia: lung infection causing chest pain, coughing, fever and fatigue		√	
Urinary tract infection: burning sensation when urinating, cloudy or bloody urine, strong odour		√	
High blood pressure (hypertension): headaches, dizziness, blurred vision, chest pain or shortness of breath		√	
Low blood pressure (hypotension): fainting, dizziness or light-headedness with standing		√	
Decrease in number of red blood cells (anemia): dizziness, feeling tired and weak, loss of energy, shortness of breath		√	
Diarrhea: loose or watery and frequent stools		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE			
Pyrexia: fever		√	
Seizures (fits or convulsions)		√	
Sepsis (serious infection)		√	
Vomiting		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep out of reach and sight of children.

Store between 15-30 ºC. Do Not Freeze.

If you want more information about MONOFERRIC:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.pfizer.ca, or by calling 1-800-463-6001.

This leaflet was prepared by Pharmacosmos A/S.
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