Public Assessment Report
Scientific discussion

Monofer 100 mg/ml solution for injection/infusion
(iron(III) isomaltoside 1000)

SE/H/734/01/DC

This module reflects the scientific discussion for the approval of Monofer. The procedure was finalised on 26 November 2009. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Pharmacosmos A/S has applied for a marketing authorisation for Monofer 100 mg/ml solution for injection/infusion.

The active substance is iron(III) isomaltoside 1000. Iron carbohydrate complexes are used in the parental treatment of iron deficiency states. The iron isomaltoside complex is characterized by a strong colloidal complex of a ferric core surrounded by isomaltoside chains resulting in a gradual release of iron. Isomaltoside 1000 consists predominantly of 3-5 glucose units and originates from a chemical modification of isomalto-oligosaccharides present in Dextran 1 Ph.Eur. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Monofer is a sterile solution for injection/infusion containing 100 mg/ml of iron as iron(III) isomaltoside 1000. The excipients of the formulation are water for injections as solvent and hydrochloric acid or sodium hydroxide for pH adjustment. The product is presented in glass vials or ampoules.

II.2 Drug Substance

Iron(III) isomaltoside 1000 has no monograph in the Ph Eur. The drug substance is a dark reddish brown powder which is freely soluble in water in the pH range 5.0-7.0 and insoluble in ethanol and other organic solvents. The structure of iron(III) isomaltoside 1000 has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been satisfactorily described and suitable specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period approved.

II.3 Medicinal Product

Monofer is formulated using excipients described in the current Ph Eur. All raw materials used in the product comply with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the drug substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the finished product specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and the data presented support the shelf life claimed in the SPC. No special storage precautions are considered necessary.

III. NON-CLINICAL ASPECTS

Due to limited non-clinical data on Monofer, the Applicant refers to studies with iron dextrans and other parenteral iron compounds.

III.1 Pharmacology

Monofer was administered to anemic piglets at three weeks of age and this was sufficient to resolve the anaemic state over one week. No adverse events were observed when using Monofer. No other pharmacodynamic studies with Monofer have been performed. The potency of iron-dextran in treating anaemic animals was presented as literature reference studies.

Monofer was not used in any secondary pharmacodynamics study. The Applicant refers to literature studies in which iron-dextrans were used on rats and rabbits. These studies show iron-dextran effects on atherosclerosis, inflammatory diseases and bone. These effects are usually seen due to iron overloading.

Monofer was not used in any safety pharmacodynamics study. The Applicant refers to several literature safety studies in which iron-dextrans were used on gerbils, guinea pig, mice, rat and beagle. These studies show iron-dextrans effects on liver, heart, kidneys, arterial pressure and immunization.

There is a long term clinical experience with iron dextran why no additional data/studies are called for.

III.2 Pharmacokinetics

Monofer has not been used in any pharmacokinetic studies. However, absorption, distribution and metabolism are well characterized in the literature for both iron and various dextrans. In piglets treated orally with iron-dextran most of the iron is trapped in the distal part of the small intestine before being pioncytosed in to the lymphatic system. This iron-dextran store is subsequently slowly released to the liver and spleen in which iron-dextran is taken up by the reticuloendothelial system before being slowly released. After intramuscular injection of iron dextran, the path of absorption depends upon the molecular size of the injected substance. Low molecular weight complexes are absorbed directly into the blood stream, while high molecular weight complexes enter the lymphatic system. When the iron is released from the dextran, within the reticuloendothelial cells, it is either incorporated into stores or transported via transferrin to the erythroid marrow. Iron then binds to bone marrow receptor sites for haemoglobin synthesis.

After intravenous infusion, dextrans with a molecular weight less than 50,000 Daltons are excreted unchanged by the kidneys. Dextrans with a higher molecular weight are slowly metabolized to glucose. Small amounts of dextrans are excreted into the gastrointestinal tract and eliminated in the faeces.

Iron injected intravenously has been shown to cross the placenta in rhesus monkeys, where some 4-5% of the total injected iron can be found in the foetuses.

Considering the long term clinical experience with iron dextran, pharmacokinetic studies with Monofer are not required.

III.3 Toxicology

Monofer has not been used in any of the presented toxicology studies. However, it is commonly recognized that iron ions are very toxic because they catalyse generation of free oxygen radicals and denaturation products. Iron is toxic if accumulated in parenchymal cells such as hepatocytes whereas cells of the reticuloendothelial system such as Kupffer cells are much less vulnerable. Complex bound iron as iron dextran and the physiological water soluble ferritin is non toxic. Dextran with a higher molecular weight than dextran 1 can cause immediate life threatening anaphylactic reactions and the iron-dextran complex can also cause allergic reactions.

High doses of up to 1000 mg Fe/kg body weight given intravenously or intraperitonial to mice or rats only caused minor damage to the liver. Iron (III) hydroxide dextran has a low toxicity and LD_{50} in mice is >2500 mg iron/kg. The repeat-dose study of rats and rabbits referred to (Golberg et al 1957) included groups of rats and rabbits given 75mg Fe /kg (as iron dextran) up to 36 times. Effects seen included siderosis of liver, spleen and lymph nodes. Additionally, 7 out of 26 rabbits died.

Both iron-dextran (very high doses of 1000-4000 mg iron/kg) and dextran itself induced micronoduli in the micronucleus bone marrow test without a dose relationship. Following repeated intramuscular iron dextran injections mice, rats, rabbits and hamsters developed injection site tumours but not tumours distant from the injection site. The majority of these tumours were sarcomas. The suspicion that iron intramuscular dextran injections could cause sarcomas in humans has not been confirmed. There are no reports for the last 20 years of sarcoma development in patients treated with iron dextran.

Iron dextran has been shown to be teratogenic and embryocidal in mice, rats, rabbits, dogs and monkeys. Foetal and maternal toxicity has been reported in monkeys at a total intravenous dose of 90 mg iron/kg. Similar effects were observed in mice and rats on administration of a dose of 125 mg iron/kg. Foetal abnormalities were observed in rats and dogs after administration of doses of 250 mg iron/kg and higher.

Generally, rabbits seemed to be more susceptible to iron induced toxicity then mice and rats.

Considering the similarity to other parenteral iron compounds, and the long clinical experience with these compounds, the lack of studies with Monofer is acceptable.

III.4 Ecotoxicity/environmental risk assessment

No studies are presented by the applicant. Monofer consists of isomaltoside 1000 (carbohydrate) and iron, which is abundant in nature. It is agreed that the use of Monofer will not pose an environmental risk.

IV. CLINICAL ASPECTS

IV.1 Introduction

The use of iron carbohydrate complexes in the parental treatment of iron deficiency states is well established. The currently available parenteral iron preparations are generally considered equally efficacious but vary in molecular size, degradation kinetics, bioavailability, toxicology, and adverse events.

Low molecular weight and high molecular weight iron dextran are commercially available. The iron dextran compounds as well as iron carboxymaltose are characterized by a strong colloidal complex of a ferric core surrounded by a carbohydrate moiety. Iron release from these compounds is gradual which implies a good toxicological profile, thus allowing it to be administered in high doses as a total dose infusion (TDI). However, the potential for anaphylactic reactions has been a concern for the clinical use of in particular high molecular weight iron dextran and a test dose is necessary according to the SmPC of Cosmofer, which is a low molecular weight iron dextran.

The acute and long term toxic properties of iron gluconate and iron sucrose necessitate the development of new iron compounds with a comparable efficacy but a superior short and long term safety profile allowing fast administration of high doses. If possible, full iron repletion during one single total dose IV infusion with a short infusion time should be provided. Additionally, a compound where it is not necessary to provide a test dose is warranted.

Dextran 1, the carbohydrate fraction used in the production of isomaltoside 1000, is indicated for the prevention of anaphylactic reactions to clinical dextran infusions for plasma volume expansion. The rationale for developing Monofer was that, theoretically, the risk for anaphylactic/anaphylactoid or delayed allergic reactions may be reduced with Monofer compared to marketed iron dextrans.

IV.2 Pharmacokinetics

There is no pharmacokinetic data specific for Monofer. Regarding pharmacokinetic properties of iron-dextran complexes, the Applicant refers to literature data. The pharmacokinetic studies referred to were mainly performed with radio-labelled iron-dextran complexes, using a radioactive iron isotope, and therefore describe the faith of the complete complexes and/or the iron component. The lack of specific pharmacokinetic data for Monofer is acceptable.

IV.3 Pharmacodynamics

There are no new pharmacodynamic data for Monofer.

IV.4 Clinical efficacy

The assessment of efficacy was based on bibliographical data in combination with data from two clinical studies. The main purpose of the studies was to establish the safety profile of the product, efficacy being a secondary endpoint.

Type of Study	Study Identifier	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Product; Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety and Efficacy	P-CKD-01	Sec. 5.3.5.2 (combined study report for P-CKD-01 and P-CHF-01)	Primary objective: Safety reassurance Secondary objective: Efficacy	Prospective open-label non comparator multi-centre	Repeated IV bolus injections of 100-200 mg iron up to 4 times or total dose infusion (TDI) up to 20 mg iron/kg	182 patients; 584 treatments	Chronic Kidney Disease (CKD) patients with a need for parenteral iron	8 weeks	Completed; Integrated CTR
Safety and Efficacy	P-CHF-01	Sec. 5.3.5.2 (combined study report for P-CKD-01 and P-CHF-01)	Primary objective: Safety reassurance Secondary objective: Efficacy	Prospective open-label non comparator multi-centre	Total dose infusion (TDI) up to 20 mg iron/kg	20 patients	Congestive Heart Failure (CHF) patients with a need for parenteral iron	8 weeks	Completed; Integrated CTR

Both studies were prospective, open-label, non-comparative studies. P-CKD-01 was conducted at 15 centres in three countries; six centres in Denmark, seven in Sweden, and two in the UK and it included 182 CKD patients in pre-dialysis or undergoing dialysis (either peritoneal dialysis (PD) or haemodialysis), who may have been treated with erythropoesis stimulating agents (ESAs) and with a need for parenteral iron due to either absolute or functional iron deficiency anaemia. P-CHF-01 was conducted at nine centres in two countries; six centres in Denmark and three in Sweden and it included 20 CHF patients with anaemia and who had a need for parenteral iron due to either absolute or functional iron deficiency anaemia.

A total of six visits were conducted during the study and the treatment period was eight weeks. The patients received Monofer either as four repeated IV boluses with 100-200 mg iron/dose at visit 2, 3, 4, and 5 or as a TDI at visit 2. If the TDI exceeded 20 mg iron/kg it was split in two and given with one week interval. Laboratory assessments (haematological (Hb, leucocytes, complete blood cell count with differentials, platelets) and biochemical (sodium, potassium, creatinine, albumin, urea, bilirubin, and ALAT) analyses) were performed at every visit. A complete physical examination was performed at visit 1 and 6, and vital signs and biochemical monitoring of treatment effects (Hb, Hct, TSAT, s-iron and s-ferritin) were performed at visit 2, 3, 4, 5, and 6. In addition, the patients in the P-CHF-01 study filled in a linear analogue scale assessment QoL questionnaire at visit 2, 5, and 6.

P-CKD-01

A total of 313 patients were screened and 182 patients entered the trial and had at least one dose of Monofer, and hence constituted the safety analysis set (intention to treat (ITT)). 16 patients were withdrawn from the trial. Five patients withdrew due to an AE, three patients due to non-compliance with protocol, and eight due to other reasons.

Biochemical laboratory parameters included in the efficacy analyses in the P-CKD-01 trial shown as mean ± SD

	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Hb (g/L) (Hb in mmol/L)	111.7 ± 11.9 (6.93 ± 0.74)	112.2 ± 12.6 (6.96 ± 0.78)	113.2 ± 12.6 (7.02 ± 0.78)	114.9 ± 12.1 (7.13 ± 0.75)	116.2 ± 12.6 (7.21 ± 0.78)
Hct	0.34 ± 0.04	0.35 ± 0.04	0.35 ± 0.04	0.36 ± 0.04	0.36 ± 0.04
TSAT (%)	21.17 ± 10.11	24.53 ± 13.66	23.44 ± 10.94	23.12 ± 9.85	23.11 ± 11.07
S-iron (µmol/L)	9.21 ± 4.01	10.54 ± 6.20	9.99 ± 4.71	9.88 ± 4.31	9.93 ± 5.05
S-ferritin (µg/L)	349.9 ± 197.8	481.9 ± 285.8	478.2 ± 266.2	441.6 ± 253.1	407.8 ± 249.0

P-CHF-01

A total of 38 patients were screened and 20 patients entered the trial and had at least one dose of Monofer, and hence constituted the ITT analysis set. Two patients were withdrawn due to other reasons.

Biochemical laboratory parameters included in the efficacy analyses in the P-CHF-01 trial shown as mean ± SD

	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Hb (g/L) (Hb in mmol/L)	108.8 ± 7.6 (6.75 ± 0.47)	110.9 ± 3.9 (6.88 ± 0.24)	112.2 ± 6.9 (6.96 ± 0.43)	109.4 ± 8.9 (6.79 ± 0.55)	112.3 ± 8.2 (6.97 ± 0.51)
Hct	0.34 ± 0.03	0.34 ± 0.02	0.35 ± 0.02	0.34 ± 0.03	0.35 ± 0.03
TSAT (%)	22.06 ± 9.72	39.50 ± 24.05	29.11 ± 11.74	30.00 ± 10.52	28.11 ± 10.46
S-iron (µmol/L)	12.47 ± 5.55	20.05 ± 10.60	14.56 ± 6.08	14.78 ± 5.06	13.79 ± 4.97
S-ferritin (µg/L)	180.0 ± 183.5	753.0 ± 326.4	645.0 ± 307.0	456.9 ± 252.2	409.7 ± 333.6

Efficacy Conclusions

In the P-CKD-01 trial, an increase in all sample estimates (Hb, Hct, TSAT, s-iron, and s-ferritin) over time as compared to baseline was indicated by the p-values. S-ferritin was significantly increased at all visits ($p < 0.0001$). Hct was not significantly increased at visit 3 but significantly increased at visit 4-6 ($p \leq 0.0026$). Hb was not significantly changed at visit 3-4 but was significantly increased at visit 5-6 ($p < 0.0001$). The largest difference in change from baseline in Hb was observed at visit 6 (8 weeks after baseline) with value of 3.9 g/L (0.245 mmol/L). TSAT was significantly increased at all visits ($p \leq 0.0220$). S-iron was significantly increased at visit 3-5 ($p \leq 0.0378$), but not at visit 6.

At a glance, the efficacy estimates (Hb, Hct, TSAT, *s*-iron, and *s*-ferritin) in the P-CHF-01 trial seemed to be increased to a higher extend at all visits compared to the P-CKD-01 trial. However, many of the results were non-significant probably due to the sparse amount of data.

Hb was increased at every visit compared to baseline; however, the increase was non-significant. The largest difference in change from baseline in Hb was observed at visit 4 (two weeks after baseline) with value of 4.7 g/L (0.294 mmol/L). Hct was significantly increased at visit 6 only ($p = 0.023$). TSAT and s-iron were significantly increased at visit 3 (TSAT: $p = 0.0006$; s-iron: $p = 0.0016$) but not at visit 4-6. S-ferritin was significantly increased at all visits ($p < 0.0001$).

The efficacy data provided in the final study report thus supports the assumption that Monofer is efficient with regards to increase in haemoglobin, at least in the CKD group.

IV.5 Clinical safety

Monofer is expected to have a similar safety profile as outlined in the Summary of Product Characteristics (SmPC) for Cosmofer. However, based on earlier clinical experiences with low molecular weight dextran fractions the incidence of dextran anaphylactoid reactions is expected to be lower. Based on the assumption that Monofer has a lower potential for anaphylactic reactions it was suggested that a test dose injection of the product should not be given before the IV application of a bolus dose or TDI of Monofer. The authorities in Denmark, Sweden and in the UK, where the Monofer trial was conducted, approved to the use of this mode of administration in the trial setting.

P-CKD-01
At visit 2 (baseline), 138 patients were given a bolus of 100 mg, 4 patients received a bolus of 100-200 mg, and 40 patients were given a TDI. The mean infusion time for the TDI was 58.8 minutes (SD: 15.9 minutes, range: 20-90 minutes). Two of the 40 patients received a TDI dose that was divided.
At visit 2, the mean dose given for TDI was 975.3 mg (SD: 238 mg, range: 462-1800 mg). The mean dose for the 4 patients receiving a bolus of 100-200 mg was 187.5 mg (SD: 25 mg, range: 150-200 mg).
In total, 584 treatments with Monofer were given (523 bolus injections of 100 mg Monofer, 17 bolus injections of 100-200 mg Monofer, and 44 TDIs).

P-CHF-01
All 20 patients received a TDI treatment with a mean infusion time of 59.8 minutes (SD: 3.6 minutes, range: 50-67 minutes). The mean dose was 868.3 mg (SD: 102 mg, range: 650-1000 mg). None of the patients received a TDI dose that was divided.
In total, 20 treatments of Monofer were given (all as TDI).

Brief Summary of Adverse Events

P-CKD-01
Related as well as non-related AEs were observed in a total of 118 out of the 182 patients (64.8 %) treated with Monofer, and a total of 244 events occurred (non-serious as well as serious events). The most frequent events were nausea, diarrhoea, infection, urinary tract infection, and dyspnoe which were observed in 4 patients (2.2 %) with a total of 5 events, pneumonia observed in 5 patients (2.7 %) with a total of 5 events, arteriovenous fistula operation observed in 4 patients (2.2 %) with a total of 6 events, pain in extremities and vomiting observed in 6 patients (3.3 %) with a total of 6 events, hypotension found in 6 patients (3.3 %) with a total of 7 events, pruritus observed in 7 patients (3.8 %) with a total of 7 events, and arthralgia observed in 7 patients (3.8 %) with a total of 9 events. Of the 244 events, 192 were non-serious AEs and 52 were SAEs. 17 non-serious AEs and 2 SAEs were classified as possible or

probable related by the investigator. In addition to these events, 6 additional SAEs have been reported but the patients were screening failures and never exposed to Monofer and were therefore excluded from the data analyses.
Eight related events occurred after first administration of Monofer, two events occurred after second administration, three events occurred after third administration, and five events occurred after fourth administration. Thus, in the present data set of 19 events there was no trend between an accumulated Monofer dose and the related event frequency.

P-CHF-01
Related as well as non-related AEs were found in a total of 13 out of 20 patients (65.0 %) treated with Monofer and a total of 25 events occurred (non-serious as well as serious events). Except for vertigo that occurred twice in a single patient, all other events occurred only once. Of the 25 events, 18 were non-serious and 7 were SAEs. None were classified as possible or probable related by the investigator.

Deaths
Two death events occurred in the P-CKD-01. Regarding one patient the investigator's diagnoses of event was pneumonia with outcome death (MedDRA coded as pneumonia). No death event was observed in P-CHF-01 trial.

Other Serious Adverse Events
There were 52 SAEs in 43 patients (i.e. 23.6 % of exposed patients) in the P-CKD-01 and seven SAEs in five patients (i.e. 25.0 % of exposed patients) in the P-CHF-01 trial.

Safety Conclusions

Based on the presented data, and compared to other parenteral iron products including Cosmofer, no significant unexpected safety findings of concern were observed when Monofer was administered as TDI or bolus injections.
No acute anaphylactic/anaphylactoid or delayed allergic reactions were observed in either CKD or CHF patients. The study was, however, not designed to detect very rare events. A possible potential for Monofer to cause anaphylactoid reactions has not been ruled out. This is sufficiently reflected in the SmPC.

IV.6 Discussion on the clinical aspects

The data from trial P-CKD-01 and P-CHF-01 are considered sufficient to support the efficacy and safety of Monofer in the treatment of iron deficiency anemia. The data is, however, insufficient to make any claims of a safety profile superior to that of other iron carbohydrate complexes. A possible potential for Monofer to cause anaphylactoid reactions, as known for other parenteral products, cannot be ruled out. This is sufficiently reflected in the SmPC.

However, based on the Applicant's responses and the study data, there is sufficient support for the proposed omission of the test dose and the recommendation of a shorter infusion time of 30-60 minutes. The SmPC has been amended with adequate warnings and instructions on precautions to ensure safe use of the product.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The risk/benefit ratio is considered positive and Monofer is recommended for approval.

User testing of the package leaflet has been performed and is acceptable.

VI. APPROVAL

The decentralised procedure for Monofer was successfully finalised on 26 November 2009.

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary
SE/H/734/01/II/24/G	The present variation is a general update of the SmPC and PIL. The main purpose of the proposed update is to simplify SmPC section 4.2 Posology and Methods of Administration, and to include the results of finalised clinical studies, which have more than doubled the clinical database. Concomitantly, the PIL is proposed generally updated to improve the readability. The submission includes 7 clinical study reports (CSRs) of which 3 CSRs are presented as voluntary PASS (IDA-03, CDK-04, IDA/CKD-EXT-01) specific for Monofer.	Yes	2020-02-20	Approval	The SmPC section 4.2 was updated regarding dosing instructions and further editorial changes for enhanced readability. In addition, minor amendment was made to section 4.8 and 5.1 based on new clinical data.

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)