LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Diafer
(iron(III)isomaltoside 1000)

SE/H/1164/01/DC

This module reflects the scientific discussion for the approval of Diafer. The procedure was finalised on 14 February 2013. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Pharmacosmos A/S has applied for a marketing authorisation for Diafer solution for injection 50 mg/ml.

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 resulting in a gradual release of iron. The complex forms a stable matrix type structure with about 10 iron(III) atoms to one molecule of isomaltoside pentamer. The isomaltoside 1000 component of Diafer consists of 3-5 glucose units with an average molecular weight of approximately 1000 kDa. It has a linear, unbranched molecular structure

The applicant already holds a marketing authorisation in the EU for the same active substance but with a different strength (100 mg/ml), approved via the decentralised procedure, SE/H/734/01/DC Monofer solution for injection 100 mg/ml.

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Diafer is a sterile solution for injection containing 50 mg/ml of iron as iron(III) isomaltoside 1000. The excipients of the formulation are water for injections as solvent, sodium chloride as tonicity agent, and hydrochloric acid or sodium hydroxide for pH adjustment. The product is presented in glass 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

Diafer 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 and storage conditions claimed in the SmPC.

III. NON-CLINICAL ASPECTS

III.1 Introduction

No non-clinical studies have been performed with Diafer. Instead a non-clinical overview and a summary for MonoFer were submitted. This is acceptable since Diafer is a further development of the approved medicinal product MonoFer and is manufactured from the same active substance using equivalent manufacturing methods. Due to limited non-clinical data on iron isomaltoside 1000 (100 mg/ml), references were also made to studies with other parenteral iron compounds.

III.2 Pharmacology

Iron isomaltoside 1000 (100 mg/ml) 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 iron isomaltoside 1000 (100 mg/ml). No other pharmacodynamic studies with iron isomaltoside 1000 (100 mg/ml) have been performed. The potency of iron-dextran in treating anaemic animals was presented as literature reference studies.

Diafer or Monofer was not used in any secondary pharmacodynamics study and references were instead made 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, effects usually seen due to iron overloading.

Diafer or Monofer was not used in any safety pharmacology study. However, several literature safety studies in which iron-dextrans were used on gerbils, guinea pig, mice, rat and beagle were presented. These studies show iron-dextrans effects on liver, heart, kidneys, arterial pressure and immunization.

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

III.3 Pharmacokinetics

No non-clinical pharmacokinetic studies have been performed with Diafer or Monofer. 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 pinocytosed 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 ~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 Diafer are not required.

III.4 Toxicology

Iron isomaltoside 1000 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 Diafer is acceptable.

III.5 Ecotoxicity/environmental risk assessment

Diafer consists of isomaltoside 1000 (carbohydrate) and iron, which is abundant in nature. Diafer is therefore not expected to pose a risk to the environment.

III.6 Discussion on the non-clinical aspects

No non-clinical studies have been performed with Diafer and only limited non-clinical data on the already approved product Monofer, which is manufactured from the same active substance using equivalent manufacturing methods, was presented. Non-clinical data presented was also obtained from literature with references to studies with iron dextrans and other parenteral iron compounds. Considering the similarity to other parenteral iron compounds, and the long clinical experience with these compounds, the lack of non-clinical studies with Diafer is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

Diafer has been developed to facilitate the administration of intravenous doses of iron in the range of 50 mg to 200 mg, which are often applied in patients on dialysis. The indication is therefore restricted to this population.

IV.2 Pharmacokinetics

One PK study has been performed with iron isomaltoside 1000 where 100 mg and 200 mg IV bolus injections were administered to 12 subjects with inflammatory bowel disease. The PK was found to be approximately dose linear for the studied doses and $t_{1/2}$ for bound s-iron was estimated to about 0.9 days (21.6 hours). Only very small quantities of iron was eliminated in urine (≈ 1 % of the dose administered).

Regarding general pharmacokinetic properties of iron-dextran complexes, circulating iron dextran is removed from plasma by cells of the reticuloendothelial system, mainly in the liver, which splits the complex into its components of iron and dextran. In a study (Beranano et al 2000) it was found that the released iron is sequestered by ferritin or removed from the cytoplasm by the action of intracellular iron transporters such as Fe-ATPase. The faith of the remaining dextran, which is a polyglucose molecule, appears to be unclear. It is suggested that it is either metabolised or excreted.

In conclusion, the PK presented by the applicant is considered acceptable.

IV.3 Pharmacodynamics

There are no new pharmacodynamic data for iron isomaltoside 1000.

IV.4 Clinical efficacy

The assessment of efficacy was based on bibliographical data in combination with data from two clinical studies. The clinical data was obtained with iron isomaltoside 1000 (100 mg/ml). 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 iron isomaltoside 1000 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 iron isomaltoside 1000, 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 iron isomaltoside 1000, 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 iron isomaltoside 1000 is efficient with regards to increase in haemoglobin, at least in the CKD group.

IV.5 Clinical safety

Iron isomaltoside 1000 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, iron isomaltoside 1000 was developed with the expectation to lower the incidence of anaphylactoid reactions. Anaphylactoid reactions are very rare but often very serious when they occur. The submitted studies were only designed to give some reassurance that iron isomaltoside 1000 does not cause any unexpected adverse events as there was no previous experience in humans.

In addition to the clinical safety data on iron isomaltoside 1000, a review of bibliographical data discussing important known safety issues for parenteral iron dextran products has been presented.

Anaphylactoid reactions are a well known safety issue with iron dextran products. The omission of the test dose has been previously accepted for iron isomaltoside 1000 (100 mg/ml) as this procedure is not expected to eliminate the risk of anaphylactoid reactions since rapid reactions would occur also with the test dose. This is supported by the data by Fishbane et al (1996) where five out of ten reactions occurred when the test dose was given indicating that the test dose procedure is not suitable for risk minimisation. Therefore parenteral iron products should only be given in settings where resuscitative medication is available.

Data has been provided showing that although patients with dextran antibodies could be given iron dextran products, patients at risk of developing hypersensitivity reactions to iron dextran cannot be identified by measurement of antibodies.

In the study by Laman et al (2005), potentials predictors for adverse (anaphylactoid reactions) were investigated. Only history of drug allergy was found to be closely related to AEs. However, it is not stated whether other allergies were included among potential predictors. The contraindication for use of iron isomaltoside 1000 in patients with a history of asthma, eczema or atopic allergies in the SmPC is maintained to keep the section in line with the contraindications for Monofer.

Data has also been presented, indicating that there may be differences in the incidence of adverse reactions between different iron dextran formulations. The data are, however, based on reported events and are therefore difficult to interpret since the reporting pattern may differ. Of note, hypersensitivity reactions are observed with all formulations, thus the data are not sufficient to withdraw currently given recommendations and warnings with regards to the use of iron isomaltoside 1000 (100 mg/ml).

The stronger binding of iron in iron dextran formulations reduces the risk of acute iron toxicity. Long-term use of iron products may lead to accumulation of iron eventually leading to haemosiderosis. Adequate information is included in section 4.9 of the SmPC.

Although the data presented does not indicate an association between iron supplementation and infectious diseases, the data from the in vitro studies support the current recommendations in section 4.4 of the SmPC, that parenteral iron supplementation should be used with caution in case of acute or chronic infections.

The use of parenteral iron products has been associated with worsening of synovial inflammation in patients with rheumatoid arthritis. Adequate contraindications and warnings are included in the SmPC in section 4.3 and 4.4.

Clinical safety data with iron isomaltoside 1000

Patient exposure

An overview of trials included in the integrated clinical safety summary is given in the table below.

	Patients exposed	Number of treatments	Mean cumulative dose	Single doses range
Open studies				
P-CKD-01	182	584	529 mg	100 mg -1800 mg
P-CHF-01	20	20	868 mg	650mg-1000 mg
COSMOS-01	12	23	300 mg	100mg -200 mg
P-IBD-01 (ongoing)	35	63	921 mg	250 mg-1000 mg
Total	**249**	**690**		**100 mg-1800 mg**

The main purpose of the already finalized phase III studies was to establish the safety profile of the product in relevant populations. Both pivotal studies (P-CKD-01 and P-CHF-01) were prospective, open-label, non-comparative in three European countries. In addition, safety has been monitored in a pharmacokinetic study (COSMOS-01) and in an ongoing comparative study in inflammatory bowel disease (IBD) patients.

P-CKD-01

Study P-CKD-01 included 182 CKD patients with a need for parenteral iron. The majority of the CKD patients (n=161) were undergoing haemodialysis most patients (n=150) being treated with ESA.

Study drug related as well as non-related adverse events, were observed in 118 out of the 182 patients treated with iron isomaltoside 1000. In total, 244 AEs were observed in 118 subjects. AEs reported in ≥ 2% of subjects include: arthralgia (3.8%; n = 7), pruritus (3.8%; n = 7), vomiting (3.3%; n = 6), pain in extremity (3.3%; n = 6), hypotension (3.3%; n = 6), diarrhoea (2.2%; n = 4), nausea (2.2%; n = 4), infection (2.2%; n = 4), urinary tract infection (2.2%; n = 4), dyspnoea (2.2%; n = 4), and arteriovenous fistula (2.2%; n = 4) .

There were 192 non-serious AEs, of which 17 were treatment-related. Among the treatment related AEs, 5 were mild, 10 were moderate, and 2 were severe (headache and hemorrhagic cyst). The most frequent treatment- related events were gastrointestinal reported in 6 patients (7 events). The remaining 175 non-serious AEs were considered unlikely, unknown, or not related to study drug.

There were 52 serious AEs (SAEs) reported in 43 subjects, of which two (mild sepsis with Staphylococcus aureus and mild unstable angina) were possibly treatment related. Both events were considered as unlikely related to study drug by the medical monitor. The remaining SAEs were considered unlikely or not related to study drug.

The 19 treatment-related events (17 non-serious AEs and 2 SAEs) were reported in 13 (7.1 %) subjects including 12 (92.3 %) who received bolus injections of 100 mg and 1 (7.7 %) who received a TDI of 1400 mg. Three subjects (1.6 %) reported >1 treatment-related event:

subject 1005 had 2 events of nausea, subject 1021 had diarrhoea, influenza, hyperhidrosis, low serum-ferritin, and arthralgia, and subject 2021 had hemorrhagic cyst and pruritus.

There were 2 deaths which were considered unrelated to study drug (one each due to unknown cause and pneumonia).

An analysis of AEs by method of administration (bolus vs. TDI), noted that 10% (n = 4) of patients who received TDI dosing reported pruritus and vomiting. However, none of the events were considered possibly or probably related to study drug. There were no AEs considered by the investigator to be possibly/probably related to study drug with an incidence ≥ 5% in the total population of 182 patients.

In the present data set, there was no trend between an accumulated iron isomaltoside 1000 dose and treatment-related event frequency of AEs.

P-CHF-01

Study P-CHF-01included 20 chronic heart failure patients who were treated with iron isomaltoside 1000 given as a high single dose infusion.

A total of 25 AEs were reported in 13 (65.0%) subjects. There were 18 non-serious AEs and 7 SAEs. None of AEs or SAEs were considered by the investigator as related to study drug and none were severe. Except for vertigo that was reported twice in a single patient, all other events occurred only once.

No death event was observed in P-CHF-01 trial.

In the present data set, there was no trend between an accumulated iron isomaltoside 1000 dose and treatment-related event frequency of AEs.

COSMOS-01

In an open-label, randomized, cross-over, single centre, PK trial 100 mg and 200 mg IV bolus injections of iron isomaltoside 1000 were given to 12 subjects with inflammatory bowel disease.

A total of 43 AEs were reported in 9 subjects. AEs reported in more than 1 subject included nausea (33%; n = 4), tachycardia (25%; n = 3), abdominal pain upper (17%; n = 2), injection site irritation (17%; n = 2), dizziness (17%; n = 2), and flushing (17%; n = 2).

Thirty-one AEs were considered study drug related including 11 AEs reported in one subject in connection to a reaction that lead to withdrawal from the study. The majority of AEs were mild. There were two severe AEs (abdominal pain and flushing) reported in a single subject which led to withdrawal from the study. Three AEs were local irritations, and only two of these were considered related to the trial drug. Review of AEs reported according to dose level shows a similar reporting frequency and severity for both the 100 mg dose as well as the 200 mg dose.

The following AEs were only reported as related (probably or possibly) to trial drug (no. of subjects/no events): back pain (1/1), chest discomfort (1/1), dizziness (2/4), dysguesia (1/1), dry mouth (1/1), feeling cold (1/1), flushing (3/4), nausea (4/5), sensation of foreign body (2/2), sensory disturbances (1/1) and tachycardia (3/4).

There were no deaths, no SAEs or other significant AEs reported.

Laboratory findings (all studies)

There were no clinically relevant changes in vital signs, electrocardiograms, physical exam clinical chemistry or safety hematology data observed over the course of the studies.

Clinically significant individual changes were per definition reported as AEs. Except for three reports of changes in s-ferritin reported as AEs none of the reported AEs included possible or probable related changes in clinical chemistry, WBC, or platelets.

Immunological events (all studies)

No acute anaphylactic/ anaphylactoid or delayed allergic reactions were observed in either CKD, CHF or IBD patients.

P-IBD-01: Interim clinical safety data

In an ongoing trial P-IBD-01, 31patients have as of a cut off date for an interim analysis (16.06.2010) been randomised to 1000 mg iron isomaltoside 1000 given over an infusion time of 15 min. Additional 35 patients have as of the cut off been randomised to 500 mg bolus injections over 2 minutes.

Three adverse drug reactions (possibly/probably related to iron isomaltoside 1000) were observed. All of these were non-serious reactions which did not reoccur upon next administration. Two subjects developed skin rashes both of which were mild in severity. The third patient experienced hypertension which was of moderate severity. All the 3 adverse events recovered without sequelae. After data lock point, a serious adverse event has been reported from the ongoing trial in IBD consisting of loss of consciousness accompanied by a generalized tonic clonic seizure occurring in close temporal relation to infusion, which was rated as possibly related due to the fact that other suspected causes (e.g. hypoglycaemia) were also listed by investigator. No conspicuous clinically significant changes in vital or clinical safety laboratory values have been observed.

Integrated safety analysis

An integrated safety data analysis of iron isomaltoside 1000 doses administered across the 3 completed studies (P-CKD-01, P-CHF-01 and COSMOS-01) showed a total of 28 related events reported by 214 exposed patients. No signs of dose related adverse events were observed. Hence, a logistic regression analysis on any adverse event (yes/no) with the dose as covariate did not show any tendency of an increase in the incidence of adverse events with higher doses. Similar reporting rates (13 %) were observed in patients receiving TDI (Total Dose Infusion) and in those receiving bolus doses.

The majority of related AEs were reported only once with the exception for nausea (n=7, 3.3 %), tachycardia (n=3, 1.4 %), abdominal pain, upper (n=3, 1.4 %) and serum ferritin decreased (n=2, 0.9 %). No new or unexpected AEs have been observed in the integrated analysis.

Post-marketing experience

Iron isomaltoside 1000 (100 mg/ml) was launched in Denmark in June 2010. Three semi-annual Period Safety Update Reports (PSURs) have been submitted for iron isomaltoside 1000 with latest report covering the period 21 December 2010 to 30 June 2011.

No safety concerns have been identified. As of October 31, 2011, the total number of doses sold was 48.100 (100 mg equivalents) and a total of 12 adverse reactions have been reported of which 7 were reported as serious. No anaphylactic reactions have been reported.

Safety conclusions

The intention with the submitted clinical studies was to provide some reassuring documentation that supports that iron isomaltoside 1000 will not lead to unexpected adverse events in humans.

The safety data indicate that the safety profile of iron isomaltoside 1000 is rather similar to that of other parenteral iron solutions. No unexpected AEs have occurred in the CKD or the CHF population. Six CKD patients experienced hypotension which is known to be associated with

rapid iron infusion. Many of the reported AEs appear to be related to the underlying disease and rather few were judged by the investigators to be related to treatment.

The occurrence of SAEs in the investigated patient populations is not unexpected due to the high age of the participants and the underlying diseases. There have been concerns regarding the relationship between IV iron and risk of infections due to the effect of iron preparations on bacteria in vitro. However, in studies where adjustment for pre-existing co-morbidities has been done, no relationship between iron administration, iron stores and infectious complications has been demonstrated.

The reporting of AEs was higher in study COSMOS-01 than in studies P-CKD-01 and P-CHF-01 and a higher proportion of the AEs were considered study related. One single patient, however, contributed with a total of 11 events and subsequently discontinued. Among the AEs probably or possibly related to study drug, no unexpected AEs were observed.

The ongoing study P-IBD-01 investigates a different posology with higher doses given over a shorter time period than recommended in the current application. No unexpected AEs have been observed, however, data are still very limited.

No anaphylactoid reactions have been observed within the clinical studies this far. However, as the studies were not designed to detect very rare events, this does not rule out a potential for iron isomaltoside 1000 to cause anaphylactoid reactions.

The post-marketing safety data reported for iron isomaltoside 1000 (100 mg/ml) so far is in accordance with the reference safety information; however, the post-marketing experience is still limited.

IV.6 Discussion on the clinical aspects

The use of iron dextrans and other iron carbohydrate complexes is well established. The assessment of efficacy is mainly based on bibliographic data since it can be concluded that the efficacy of all iron carbohydrate complexes is related to the concentration of elemental iron in a given complex rather than the nature of the iron carbohydrate complex in question.

The efficacy data from trial P-CKD-01 and P-CHF-01 supports the assumption that iron isomaltoside 1000 is efficient with regards to increase in haemoglobin.

The use has been restricted to patients on dialysis with the justification that Diafer has been developed to facilitate the administration of doses in the range of 50 mg to 200 mg, often applied in this population.

The safety data indicate that the safety profile of iron isomaltoside is comparable to that of iron dextran products. No acute anaphylactic/anaphylactoid or delayed allergic reactions have been observed within the clinical study program this far. The exposed populations are, however, still too small to detect very rare events and a potential for iron isomaltoside 1000 to cause anaphylactoid reactions cannot be ruled out.

No new data has been provided with the current application to support any changes in the safety information as compared to the information given in the SmPC of Monofer; therefore the SmPC for Diafer has been kept in line with that of SE/H/734/01/DC Monofer.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to the product CosmoFer 50mg/ml solution for infusion and injection. The bridging report submitted by the applicant has been found acceptable.

The risk/benefit ratio is considered positive and Diafer solution for injection 50 mg/ml is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Diafer solution for injection 50 mg/ml was successfully finalised on 14 February 2013.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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