EDITORIAL

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Iron isomaltoside 1000: a new high dose option for parenteral iron therapy

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ABSTRACT

Iron isomaltoside 1000 (Monofer®) is a new dextran-free parenteral iron product, currently approved in 22 EU countries. Iron isomaltoside 1000 consists of iron and a carbohydrate moiety where the iron is tightly bound in a matrix structure, which enables a controlled and slow release of iron to iron-binding proteins, avoiding toxicity. The carbohydrate, isomaltoside 1000, is a purely linear chemical structure with low immunological activity. Due to the structure of iron isomaltoside 1000 and the low anaphylactic potential, there is no requirement for a test dose, and it can be administered in high doses with a maximum dosage of 20 mg/kg within 30-60 minutes in one visit. Thus, iron isomaltoside 1000 offers the broadest dosage range compared to other parenteral iron products on the market. Due to the dose flexibility, the possibility of providing full iron correction in one single visit makes iron isomaltoside 1000 highly convenient for both the health care professional and the patient. Clinical studies of iron isomaltoside 1000 show that it is an effective and well-tolerated treatment of iron deficiency anaemia with a favourable safety profile. Furthermore, iron isomaltoside 1000 does not seem to induce hypophosphataemia.

Key-Words:
High dose; iron deficiency anaemia; iron isomaltoside; iron treatment.

INTRODUCTION

The ability to give high doses of iron is important in the management of iron deficiency anaemia (IDA) in a number of clinical conditions where demands for iron are high, such as chronic kidney disease (CKD), chronic blood loss associated with inflammatory bowel disease (IBD) or other gastrointestinal disease, pregnancy, and blood loss during surgery. Parenteral iron offers a fast iron correction, and it is superior to oral iron in many circumstances, especially in the treatment of anaemia associated with chronic diseases where the patients may be intolerant of oral iron or because the iron absorption may be blocked, in cases with large iron deficits as the maximum capacity for oral iron absorption is very limited, or when patients are treated with erythropoiesis-stimulating agents (ESAs).

The currently available parenteral iron preparations include high molecular weight iron dextran (Dexferrum®), low molecular weight iron dextran (Cosmofer®/Infed®), iron gluconate (Ferrlecit®), iron sucrose (Venofer®), ferumoxytol (Feraheme®), iron carboxymaltose (Ferinject®/Injectafer®), and iron isomaltoside 1000 (Monofer®). They are generally considered equally efficacious, but most of them have limitations in dosing, administration (duration and frequency), and safety profile. High molecular weight iron dextran has been associated with an increased risk of anaphylaxis/anaphylactoid reactions and is not available in

Europe[1-5]. These side effects are significantly reduced with low molecular weight iron dextran[1-4], but this still requires a test dose and has a long infusion time of four to six hours for larger doses[6]. Iron gluconate, iron sucrose, and ferumoxytol (only available in US and use limited to CKD patients) can only be administered in moderate doses since they are limited to a maximum total single dose of 125 mg, 200 mg, and 510 mg, respectively[7-9]. In addition, treatment with iron sucrose requires a test dose in Europe[8], and it has been found associated with acutely increased proteinuria at 100 mg weekly infusions[10,11]. Iron gluconate has also been found to be associated with a mild transient proteinuria in CKD patients[11].

Iron carboxymaltose does not require a test dose, and it can be administered in doses of 20 mg/kg up to a maximum of 1000 mg per infusion[12]. Iron carboxymaltose infusion has been associated with hypophosphataemia of unknown aetiology. The clinical significance of the hypophosphataemia is unknown[13].

The newest parenteral iron preparation, iron isomaltoside 1000 (Monofer®), was introduced in Europe in 2010. The ambition with iron isomaltoside 1000 was to develop an efficacious parenteral iron product with a favourable safety profile without test dose requirement and without dose limitations in order to optimise dosing flexibility and user convenience. Iron isomaltoside 1000 fulfils these requirements and can be administered with a maximum dosage of 20 mg/kg, no test dose, and within 30-60 minutes in a single visit[14]. Due to the dose flexibility that iron isomaltoside 1000 offers, the possibility of providing full iron correction in a single infusion makes it highly convenient for both the health care professionals and the patient. The present review describes the physiochemical characteristics, pharmacological, pharmacokinetic, and immunogenic properties, preclinical and clinical data, and cost analysis of iron isomaltoside 1000.

PHYSIOCHEMICAL CHARACTERISTICS OF IRON ISOMALTOSIDE 1000

Iron isomaltoside 1000 consists of iron and a carbohydrate moiety. The carbohydrate isomaltoside 1000 consists predominantly of 3-5 glucose units and originates from isomalto-oligosaccharides produced by hydrolysis of dextran, followed by subsequent fractionation and chemical modification to provide a product with the desired molecular weight distribution. Furthermore, isomaltoside 1000 is isolated after chemical reduction of the reducing sugar residues to avoid complications due to redox reactions or degradation of the aldehyde group at the anomeric centre. The absence of reducing sugar prevents any complex redox reactions and thereby degradation of the iron complexes[16]. Apart from differences in molecular weight between dextran in iron dextran and isomaltoside 1000, the latter is also completely devoid of any branching structures as evidenced by ^{13}C and ^{1}H NMR spectroscopic analysis and it does not contain any reducing sugar residues[15]. Thus, although isomaltoside 1000 is manufactured by a chemical modification and hydrolysis of dextran, isomaltoside 1000 is not a dextran. The chemical structure of isomaltoside 1000 is very different from the dextran structure, in which the α-(1,3) linked branches of the molecule are wound around the main chain α-(1,6) linked polymer in a tight helical arrangement[15] while isomaltoside 1000 has a purely linear oligomer structure of α-(1,6) linked glucopyranose residues, on average repeating 5.2 times, and contains no reducing sugar units.

Electron microscopy[16] presented the nano structure of iron isomaltoside 1000 as spheroidal while ^{13}C NMR and associated molecular modelling have indicated that it is composed of a matrix structure in which the iron atoms are predominantly bound and dispersed in the matrix. From the masses of the components it can be calculated that there are approximately 10 iron atoms bound per oligosaccharide molecule. It is not yet known if these constitute coordinated single iron oxide moieties or small clusters of coordinated iron oxide. The iron isomaltoside 1000 matrix is composed of interchanging strands of linear isomaltoside 1000 with iron atoms placed in cavities between and within the isomaltoside molecules[15]. The matrix structure enables a controlled and slow release of iron which attaches to iron-binding proteins with little risk of free iron toxicity (Fig. 1). This is a unique structure and quite different from other iron products which are described as a pure iron core surrounded by a carbohydrate shell. The formation of this molecular matrix structure is possible due to the short, linear, and non-ionic isomaltoside 1000 structure combined with the production technology for complexing iron and isomaltoside 1000.

Iron is tightly bound in the iron isomaltoside 1000 molecule; assessment of an iron isomaltoside 1000

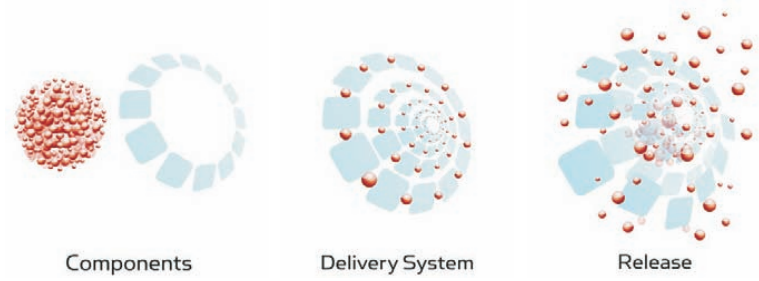

Figure 1

Matrix structure of iron isomaltoside 1000 wich enables a controlled and slow release of iron.

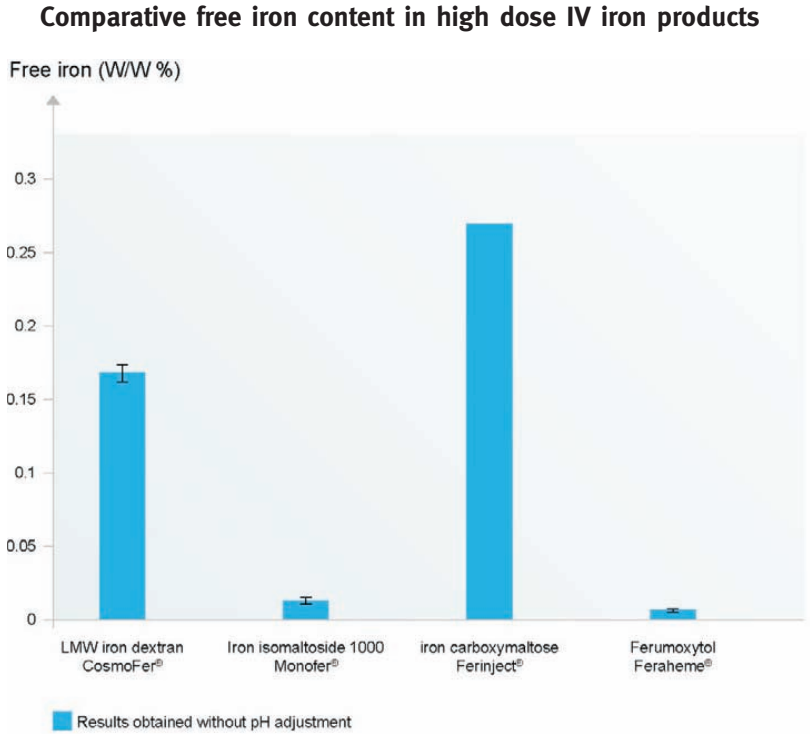

Figure 2

Free iron content in high dose parenteral iron products. The data is obtained without pH adjustment. The detection limit was 0.002 %. [Modified from Jahn *et al.*, 2011 (Ref. 16)].

solution equivalent to that administered to patients showed very low concentrations of free iron close to the detection limit of the assay (Fig. 2). A similar low concentration of free iron has been found with ferumoxytol, while the concentration of free iron in iron dextran and iron carboxymaltose solutions is significantly

higher[15]. Measurement of labile iron showed that the newer iron products (iron carboxymaltose, ferumoxytol, and iron isomaltoside 1000) have low labile iron content when compared to the older products (iron dextran « iron sucrose and iron gluconate)[15].

IMMUNOGENIC PROPERTIES OF ISOMALTOSIDE 1000

Anaphylactoid/anaphylactic reactions may occur with all parenteral iron compounds and were seen relatively often with the old high molecular weight iron dextran products. The pathogenic mechanisms for these reactions is not entirely clear, but the reactions seem to occur both through specific and non-specific immune reactions, with the carbohydrate carrier playing an important role for these reactions[16]. Thus, an important aim of the development of iron isomaltoside 1000 was to develop a product with a low risk of anaphylactoid/anaphylactic reactions. In order to achieve this, a carbohydrate carrier with a low immunogenic potential was sought. In iron isomaltoside 1000, the carbohydrate carrier, isomaltoside 1000, is based on a chemical modification of oligomers known to prevent dextran-induced anaphylactic reactions.

Since it is well known that homopolymers of glucose have very low immunogenic potential[17], in product design, any residual branching units that were α-linked to the 3-position of the main chain were removed, and the reducing sugar residue was chemically transformed quantitatively to non-reducing groups.

Thus, from a theoretical point of view, the immunogenic potential of iron isomaltoside 1000 is expected to be very low, and on this basis, the regulatory authorities decided that no test dose was required in the first clinical studies with iron isomaltoside 1000. These studies supported the theoretical rationale for low immunogenic activity, and iron isomaltoside 1000 was therefore approved for use without a test dose.

PHARMACOLOGICAL AND PHARMACOKINETIC PROPERTIES OF IRON ISOMALTOSIDE 1000

Following IV administration, iron isomaltoside 1000 is rapidly taken up by the cells in the reticuloendothelial system (RES), particularly in the liver and spleen, from where iron is slowly released. The plasma half-life is 5 hours for circulating iron and 20 hours for total iron (bound and circulating). Circulating iron is removed from the plasma by cells of the RES which split the complex into iron and isomaltoside 1000. Iron is immediately bound and stored, mainly in ferritin. The iron replenishes haemoglobin and depleted iron stores. Negligible quantities of iron are eliminated in the urine and faeces. Due to the size of the nanoparticles (20.5 nm), iron isomaltoside 1000 is not eliminated via the kidneys. The carbohydrate component, isomaltoside 1000, is either metabolised or excreted unchanged via the kidney[14].

An open-label, cross-over, single-centre study was performed in 12 patients (5 men/7 women) with inflammatory bowel disease (IBD) to assess pharmacokinetics[18]. The patients were allocated to one of two single-dose treatments where iron isomaltoside 1000 was administered as a single bolus dose of 100 or 200 mg with a four-week interval between the two doses. The dose was administered at a maximum of 50 mg of iron/minute. Pharmacokinetic (PK) variables were analysed for total iron (TI), isomaltoside-bound iron (IBI), and transferrin-bound iron (TBI) according to a one-compartment model. TI and TBI were measured by the Graphite GFAAS system and the Advia chemistry system, respectively, and IBI was calculated by subtracting TBI from TI, assuming that no free iron was present and that quantities of ferritin were negligible, so that the only iron forms present in plasma were TI, TBI, and IBI. The concentration versus time relationship for IBI and TI showed first-order kinetics with small deviations for dose-linearity, and the PK parameters for IBI were close to that of TI (Table I). Thus, TI could be used as a marker of iron isomaltoside 1000 PK in future PK studies. Only approximately 1 % of the doses administered were excreted in the urine. One of the patients was withdrawn after receiving a 100 mg dose because of abdominal pain and flushing. No serious adverse events (SAE) were reported[18].

Presently, there are several PK studies ongoing with higher doses of iron isomaltoside 1000 in different patient populations (ClinicalTrial.gov: NCT01213979, NCT01280240, NCT01213992, NCT01469078, and NCT01213680).

Table I

Geometric mean (CV in %) for PK parameters of IBI, TI, and TBI

Endpoint	Isomaltoside-bound iron		Total iron		Transferrin-bound iron	
	Treatment		Treatment		Treatment	
	100 mg	200 mg	100 mg	200 mg	100 mg	200 mg
$auc_{0\text{-}end}$ (h*µg/ml)	809 (24)	1885 (20)	894 (21)	2017 (19)	83 (19)	129 (15)
$auc_{0\text{-}inf}$ (h*µg/ml)	888 (22)	2141 (23)	1010 (19)	2319 (21)	163 (67)	228 (51)
c_{max} (µg/ml)	35.6 (39)	68.6 (26)	37.3 (38)	71.1 (26)	2.1 (30)	3.0 (16)
c_0 (µg/ml)	28.3(32)	64.5 (29)	28.9 (32)	66.8 (28)	1.7 (37)	2.9 (37)
k_e (1/h)	0.033 (12)	0.031 (24)	0.030 (15)	0.029 (23)	0.011 (85)	0.013 (87)
$t_{1/2}$ (h)	20.8 (12)	22.5 (24)	23.2 (15)	23.5 (23)	62.2 (85)	53.9 (87)
v_D based on c_0 (l)	3.5 (32)	3.1 (30)	3.5 (32)	3.0 (28)	60.6 (36)	68.3 (37)

EFFICACY AND SAFETY PROFILE OF IRON ISOMALTOSIDE 1000

In the recent past, the efficacy and safety of iron isomaltoside 1000 in the treatment of IDA has been investigated in two phase III clinical studies in patients with either chronic kidney disease (CKD) or chronic heart failure (CHF)[19,20]. The primary endpoint of these studies was to establish the safety profile of iron isomaltoside 1000, whereas efficacy was the secondary endpoint. Both were open-label, non-comparative, multi-centre studies where the patients attended six visits during a study period of eight weeks. At the investigator's discretion, iron isomaltoside 1000 was administered either as four repeated intravenous (IV) bolus injections with 100-200 mg iron per dose administered at baseline and at week 1, 2, and 4 (the last dose could be administered as total remaining dose if the total calculated iron requirement exceeded 800 mg) or as a high single iron correction dose (total dose infusion (TDI)) at baseline. If the TDI requirement exceeded 20 mg iron/kg the dose was divided into two and these given at an interval of one week. No test dose was given. The total calculated iron requirement and administered cumulative dose in each patient were based on a target Hb of 130 g/L and utilising the Ganzoni formula that reflects body weight, the difference between actual haemoglobin and target haemoglobin, and the desired level of iron stores (commonly 500 mg)[21]. The safety assessments consisted of type and frequency of adverse events (AEs) and SAEs, changes in vital signs (including electrocardiogram (ECG)), and clinical laboratory analyses (biochemistry: *s*-sodium, *s*-potassium, *s*-creatinine, *s*-albumin, *s*-urea, *s*-bilirubin, and alanine aminotransferase (ALAT), haematology: leucocytes, complete blood cell count with differentials, and platelets) 1, 2, 4, and 8 weeks after baseline. The efficacy assessments consisted of laboratory monitoring of treatment effect on haemoglobin (Hb), transferrin saturation (TSAT), and *s*-ferritin levels 1, 2, 4, and 8 weeks after baseline. In addition, the CHF study included *s*-iron, which was monitored at the same time points, and a linear analogue scale assessment (LASA) quality of life (QoL) questionnaire measuring QoL 4 and 8 weeks after baseline. The LASA is a validated QoL assessment consisting of 100-mm linear analogue scales that measured the patient's energy level, ability to do daily activities, and overall QoL.

IRON ISOMALTOSIDE 1000 ADMINISTERED TO PATIENTS WITH CHRONIC KIDNEY DISEASE

The study was conducted at 15 centres in three European countries (six in Denmark, seven in Sweden, and two in the United Kingdom). A total of 182 CKD patients (128 men/54 women) receiving dialysis (n = 161) or pre-dialysis care (n = 21) were included. The vast majority of patients were receiving haemodialysis. The patients were generally on ESA treatment (n = 82 %), and the dosage of ESA was kept constant during the study. Patients were either switched from an existing parenteral iron maintenance therapy (n = 144) or were not currently treated with parenteral iron (n = 38). The mean ± SD age was 63.3 ± 13.8 years (range: 21-91 years). Patients not receiving parenteral iron treatment when entering the study had a baseline Hb of 99.1 ± 9.0 g/L and a *s*-ferritin of 231 ± 154 µg/L, and patients who switched from a parenteral iron maintenance regimen had a baseline Hb of 114.9 ±

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