

Re-submission

iron III isomaltoside 1000 (contains 50mg iron per mL) (Diafer[®]), solution for injection
SMC No. (1177/16)

Pharmacosmos UK Limited

13 January 2017

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

iron III isomaltoside 1000 5% (Diafer[®]) is accepted for use within NHS Scotland.

Indication under review: For the treatment of iron deficiency in adults with chronic kidney disease (CKD) on dialysis, when oral iron preparations are ineffective or cannot be used.

Iron III isomaltoside 1000 at a higher (10%) concentration has been shown to be non-inferior to another intravenous iron product in maintaining haemoglobin concentration in adult patients with CKD who are iron deficient and are receiving haemodialysis.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of iron III isomaltoside 1000 5%. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

For the treatment of iron deficiency in adults with chronic kidney disease on dialysis, when oral iron preparations are ineffective or cannot be used.

The diagnosis of iron deficiency should be based on appropriate laboratory tests (eg serum ferritin, serum iron, transferrin saturation or hypochromic red cells).

Dosing Information

Up to 200mg iron may be administered at any one time with a maximum weekly dose of 1000mg. If higher doses than 200mg of iron are needed, other iron medicinal products intended for intravenous (IV) use should be used.

The iron dose must be individualised based on the clinical response to treatment including evaluation of haemoglobin, ferritin and transferrin saturation, concomitant treatment with an erythropoiesis stimulating agent (ESA) and the dose of ESA treatment. Targets may vary from patient to patient and depending on local guidelines.

Maintenance therapy with IV iron treatment may be given as small doses administered at regular intervals to maintain iron status tests stable within specific limits with the intent of avoiding development of iron deficiency or decline of iron test parameters below specific levels.

Iron isomaltoside 1000 can be administered either as an IV bolus injection or during a haemodialysis session directly into the venous limb of the dialyser. It may be administered undiluted or diluted in up to 20mL sterile 0.9% sodium chloride.

Iron isomaltoside 1000 should only be administered when staff who are trained to evaluate and manage anaphylactic reactions are immediately available, in an environment where full resuscitation facilities can be assured. Patients should be observed for adverse effects for at least 30 minutes following each injection. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Facilities for cardiorespiratory resuscitation and equipment for handling acute anaphylactic/anaphylactoid reactions should be available, including an injectable 1:1000 adrenaline solution. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.

Product availability date

April 2014

Summary of evidence on comparative efficacy

Iron III isomaltoside 1000 (henceforth referred to as iron isomaltoside 1000) solution for injection is a colloid with strongly bound iron in spheroidal iron-carbohydrate particles, forming a stable matrix type structure.¹ The formulation under review, Diafer[®], containing 50mg per mL of iron (5%), is hereafter referred to as iron isomaltoside 1000 5%. A more concentrated form of the product under review is also available: iron III isomaltoside 1000 (100mg iron per mL) (10%) (Monofer[®]) solution for

injection/infusion.² It was accepted by SMC in 2011 but was restricted to exclude patients receiving haemodialysis.

There is currently no clinical study evidence using the Diafer[®] formulation under review. The evidence is from a phase III, randomised, open-label, 6-week non-inferiority study (PROPOSE) which compared the higher, 10% strength of iron isomaltoside 1000 (Monofer[®]) with iron sucrose in 351 patients with chronic kidney disease (CKD) receiving haemodialysis.³ Patients were included if they were at least 18 years old, had a diagnosis of CKD and had been on haemodialysis therapy for ≥ 90 days, had haemoglobin (Hb) ≥ 95 g/L and ≤ 125 g/L at screening, serum ferritin < 800 micrograms/L and transferrin saturation (TSAT) $< 35\%$, ESA treatment with dose stable for the previous four weeks, IV iron not more than an average of 100mg/week for the previous four weeks and life expectancy ≥ 12 months.

Patients were randomised equally, stratified by serum ferritin (< 100 micrograms/L versus ≥ 100 micrograms/L) to receive IV injections of:

- iron isomaltoside 1000 10% 500mg at baseline (subgroup A1)
- iron isomaltoside 1000 10% 100mg at baseline and 200mg each at weeks 2 and 4 (subgroup A2)
- iron sucrose 100mg at baseline and 200mg each at weeks 2 and 4 (group B)

This resulted in a 2:1 ratio of patients treated with iron isomaltoside 1000 10% versus iron sucrose. All dosages were administered during dialysis. Treatment with ESA was to remain stable throughout the study.³

The primary outcome was the proportion of patients who maintained Hb ≥ 95 g/L and ≤ 125 g/L at week 6, analysed in the final analysis set (FAS) and per protocol (PP) populations. FAS (n=341) included all randomised patients who received at least one dose of study medication and had at least one post-baseline Hb assessment. PP (n=306) included all patients in the FAS without a major protocol deviation of clinical or statistical relevance. The proportions of patients receiving iron isomaltoside 1000 10% (in subgroup A1 or A2) versus iron sucrose who achieved the primary outcome were 83% (187/226) versus 83% (95/115) $p=0.01$ in FAS and 84% (167/199) versus 82% (88/107), in the PP population. As the results were within the 10% margin, non-inferiority of iron isomaltoside 1000 10% to iron sucrose was demonstrated.³

The subgroups receiving iron isomaltoside 1000 10% (single or split dosing) were also compared individually with iron sucrose, although these tests were not powered for non-inferiority. The proportions of patients in the iron isomaltoside 1000 10% split dosing subgroup (A2, which reflects the licensed dose) compared with patients in the iron sucrose group who achieved the primary outcome were 84% (95/113) versus 83% (95/115), in FAS, and 86% (83/97) versus 82% (88/107) in the PP population.³

After six weeks of treatment, there were no significant differences between treatment groups in the secondary outcomes of change from baseline of Hb concentration, serum iron, TSAT, serum ferritin and reticulocyte count. There was also no significant difference between treatment groups in the patients' energy levels, ability to do daily activities and overall quality of life assessed using the Linear Analogue Scale Assessment score.³

Summary of evidence on comparative safety

The rate of adverse events was comparable between subgroups A1 (single dose of iron isomaltoside 1000 10%), A2 (split doses of iron isomaltoside 1000 10%) and group B (iron sucrose): 45% (51/114), 51% (59/116) and 41% (47/114). These were considered to be serious in 7.9%, 11% and 5.3% of the respective groups. Adverse events led to study discontinuation in 2.6%, 6.8% and 0.8% of the respective groups.³

Adverse events considered to be treatment-related were reported in 5.2% (12/230) of patients receiving iron isomaltoside 1000 10%: drug intolerance, hypersensitivity, dyspepsia, malaise, muscle spasms and paraesthesia in subgroup A1 and drug intolerance, anxiety, constipation, pruritus [two events] and urticaria in subgroup A2. In group B, 2.6% (3/114) of patients receiving iron sucrose reported a total of five treatment-related adverse events (one patient reported three events): dry mouth, dyspnoea, chills, staphylococcal bacteraemia and limb discomfort).³ The proportions of serious treatment-related adverse events were 0.4% (1/230) (hypersensitivity during drug administration) in the iron isomaltoside 1000 10% group and 1.8% (2/114) (staphylococcal bacteraemia and dyspnoea during drug administration) in the iron sucrose group.³

IV iron products should only be administered when appropriately trained staff and resuscitation facilities are immediately available; patients should be closely monitored for signs of hypersensitivity during and for at least 30 minutes after every administration. In the event of a hypersensitivity reaction, treatment should be stopped immediately and appropriate management initiated. Hypotensive episodes may occur if the intravenous injection is administered too rapidly.¹

One millilitre of undiluted iron isomaltoside 1000 5% contains up to 4.6mg (0.2mmol) of sodium. This should be taken into account in patients on a sodium-controlled diet.¹

Summary of clinical effectiveness issues

Iron deficiency is common in patients with advanced CKD. In patients receiving haemodialysis, the requirement for iron is increased in order to replace blood losses and to allow erythropoiesis with ESA.⁴ Currently available treatments for the indication under review are iron sucrose (Venofer[®]) and iron dextran (CosmoFer[®]), although the latter is rarely used in this setting in practice.^{5,6} Iron isomaltoside 1000 10% (Monofer[®]) and ferric carboxymaltose (Ferinject[®]) are both licensed for the indication under review but not recommended by SMC for haemodialysis patients.

There are no clinical studies using the 5% strength of the iron isomaltoside 1000 formulation. The PROPOSE study demonstrated that the higher strength of iron isomaltoside 1000 (10%) is non-inferior to a relevant comparator, iron sucrose, in maintaining Hb concentration in adult patients with CKD who are iron deficient and are receiving haemodialysis.

A limitation of the PROPOSE study is that the dose regimen in one iron isomaltoside subgroup did not reflect the licensed dosing for the Diafer[®] formulation under review but these results were pooled with the split dose subgroup and compared with iron sucrose. Another limitation is the 6-week study duration, which is short for a potentially long-term treatment.³

Iron isomaltoside 1000 5% can be administered as an intravenous bolus injection whereas iron sucrose (Venofer[®]) requires to be administered as slow IV injections or IV infusions (iron sucrose 20mg iron per minute).^{1,5} Clinical experts consulted by SMC advised that it is unlikely that the potential reduction in administration time would be beneficial to the service. All IV iron products require that the patient be observed for adverse effects for at least 30 minutes following each injection.

Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis comparing iron isomaltoside 1000 5% to iron sucrose for the treatment of iron deficiency in patients with chronic kidney disease on dialysis, when oral iron preparations are ineffective or cannot be used. The time horizon used in the analysis was one year.

The clinical data used to underpin the assumption of comparable efficacy between iron isomaltoside 1000 5% and iron sucrose, were derived from the PROPOSE study, a phase III study which compared the safety and efficacy of iron isomaltoside 1000 10% to iron sucrose in patients with stage 5 chronic kidney disease who were on maintenance iron therapy. Based on the results of this analysis, non-inferiority was considered to have been demonstrated as the proportions of patients achieving the primary outcome were 83% (187/226) versus 83% (95/115) in the iron isomaltoside 1000 and iron sucrose groups respectively.

Drug acquisition costs and administration costs were included in the analysis. Nurse cost per hour was based on a band 6/7 nurse including the costs of obtaining nursing qualifications. It should be noted that the time to administer treatment is considered to be the key driver within the economic analysis. In the base case, iron isomaltoside 1000 5% was assumed to be administered as a 'fast push' injection over 1 minute, while iron sucrose injection and infusion were assumed to be administered over 5 and 15 minutes respectively. The maintenance dose used in the economic analysis was 55mg per week. Monitoring costs were assumed to be the same for both treatments and the cost associated with adverse events were not included, on the basis of comparable safety profiles.

A patient access scheme (PAS) was submitted by the company and assessed by the patient access scheme assessment group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered which reduced the list price of the medicine. Without the PAS, iron isomaltoside 1000 5% resulted in incremental savings versus iron sucrose injection and infusion of £193 and £1,279 respectively. The savings stem solely from lower administration costs (as a result of reduced time taken to administer treatment). With the PAS, the incremental savings associated with iron isomaltoside 1000 5% increased. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

The company provided a number of scenario analyses which varied the time to administer treatment in both arms. The assumption that iron isomaltoside 1000 5% would be administered in a shorter time than iron sucrose was not considered appropriate. Based on the assumption that both treatments require the same time to administer ie 5 minutes, iron isomaltoside 1000 5% (without the PAS) resulted in an incremental cost of £236 versus iron sucrose injection. With the PAS, iron isomaltoside 1000 5% became a cost-effective treatment option versus iron sucrose injection.

In order to address uncertainty surrounding several key variables, the company also provided a combined analysis whereby nurse cost per hour was based on band 5 (without qualification costs), administration time was 5 minutes for both treatments, an initial loading dose of 1000mg was assumed for both treatments and the maintenance dose for both treatments was assumed to be 100mg fortnightly. Based on this analysis, iron isomaltoside 1000 5% (without PAS) resulted in an incremental cost of £297 versus iron sucrose injection. With the PAS, iron isomaltoside 1000 5% became a cost-effective treatment option.

A key weakness with the previous submission was uncertainty over some of the resource-use assumptions that gave rise to the base case savings. In particular, combined scenario analysis showed that in some cases iron isomaltoside 1000 5% would no longer be considered cost-minimising. However, the revised PAS in the resubmission has meant that iron isomaltoside 1000 5% is cost-effective even in this scenario. As such, the economic case has been demonstrated.

Other data were also assessed but remain commercially confidential.*

Summary of patient and public involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from Kidney Research UK, which is a registered charity.
- Kidney Research UK has received 7.95% pharmaceutical company funding in the past two years, including from the submitting company.
- Many people with chronic kidney disease (CKD) Stage 3, 4 and 5 develop anaemia and experience symptoms including tiredness, lethargy, dyspnoea and palpitations.
- Most people with CKD will be given iron supplements because iron is needed for the production of red blood cells. To boost iron levels, iron may be given as tablets, such as daily ferrous sulphate tablets, or as intravenous infusions, sometimes during dialysis.
- Iron isomaltoside 1000 5% is as safe and effective as other IV iron treatments and appears to reduce the “metallic taste”. The full dose can also be administered as a single fast push injection, which may enhance treatment compliance and efficacy as it means that a full prescribed dose can be administered in a single injection during dialysis.
- For those in whom other available iron treatments are not suitable, iron isomaltoside 1000 5% offers an acceptable alternative.

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) national guideline “Chronic renal disease: managing anaemia” was published in June 2015 and recommends that IV iron therapy is offered to all iron deficient anaemic adults and young people receiving haemodialysis. Oral iron therapy should be offered only when intravenous administration is contraindicated or on the basis of informed patient choice. In patients receiving ESA therapy, correction to normal Hb levels is not recommended. The initial target of iron treatment is to achieve percentage of hypochromic red blood cells less than 6% (unless ferritin is greater than 800 micrograms/litre) and reticulocyte Hb count or equivalent tests above 29pg (unless serum ferritin is greater than 800 micrograms/litre). The dosage of iron required to achieve this is approximately 500 to 1000mg. Once the treatment target has been met, maintenance therapy at approximately 50 to 60mg of iron per week can be implemented. Monitoring of iron stores should be carried out every one to three months to avoid iron overload.⁷

The Scottish Intercollegiate Guidelines Network (SIGN) published a guideline on the diagnosis and management of chronic kidney disease in 2008. SIGN recommends that erythropoiesis stimulating agents should be considered in all CKD patients with anaemia however the management of iron deficiency in this patient population is not discussed.⁸

Kidney Disease: Improving Global Outcomes (KDIGO) published a Clinical Practice Guideline for Anemia in Chronic Kidney Disease in 2012. It includes recommendations on the use of IV iron therapy including iron isomaltoside.⁹

Additional information: comparators

Iron sucrose (20mg iron per mL), (Venofer[®]) solution for injection or concentrate for solution for infusion.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Iron isomaltoside 1000 5%	100mg iron every fourteen days as an intravenous bolus injection or directly into the venous line of dialysis machine	441
Iron sucrose	100mg iron every fourteen days as a slow intravenous injection, an intravenous infusion or directly (slowly) into the venous line of dialysis machine	226

Dosage regimens are individualised according to patient requirements. Regimen in table corresponds to the maintenance regimen for patients with anaemia of chronic kidney disease who are receiving erythropoiesis stimulating agents and are on haemodialysis, cited in National Institute for Health and Care Excellence 2015 guidance. Initial iron deficiency correction cumulative dose of 500mg to 1000mg is also required for most patients.⁷ Costs from MIMS online, 21 October 2016. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 2,030 patients eligible for treatment with 5% iron isomaltoside 1000 in year 1 and 2,057 patients in year 5 to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the with-PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

Other data were also assessed but remain commercially confidential.*

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Iron (III) isomaltoside 1000, (50mg iron per mL) (Diafer[®]), solution for injection. Summary of product characteristics. Pharmacosmos UK Limited. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 29 September 2014
2. Iron (III) isomaltoside 1000, (100mg iron per mL) (Monofer[®]), solution for injection/infusion Summary of product characteristics. Pharmacosmos UK Limited. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 23 November 2015
3. Bhandari S, Kalra PA, Kothari J et al. A randomized, open-label trial of iron isomaltoside 1000 (Monofer[®]) compared with iron sucrose (Venofer[®]) as maintenance therapy in haemodialysis patients. *Nephrol Dial Transplant* 2015 0: 1–13
4. Macdougall IC, Bircher AJ, Eckardt K-U et al. Iron management in chronic kidney disease: conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference *Kidney International* (2016) 89, 28–39
5. Iron sucrose (20mg iron per mL), (Venofer[®]) solution for injection or concentrate for solution for infusion. Summary of product characteristics. Vifor Pharma UK Limited. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 29 February 2016
6. Iron dextran (50mg iron per mL) (CosmoFer[®]) solution for infusion and injection. Pharmacosmos UK Limited. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 14 March 2014
7. National Institute of Health and Care Excellence (NICE). Guidance NG8: Chronic kidney disease: managing anaemia (2015). www.nice.org.uk
8. Scottish Intercollegiate Guidelines Network (SIGN). SIGN 103: Diagnosis and management of chronic kidney disease (2008). www.sign.ac.uk
9. Kidney Disease Improving Global outcomes (KDIGO) Clinical Practice Guideline for Anemia in Chronic Kidney Disease *Kidney International Supplements* (2012) 2, 279–335

This assessment is based on data submitted by the applicant company up to and including 13 December 2016.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.