North Staffordshire and Stoke-on-Trent Area Prescribing Committee

Medicine Review Summary

Monofer® : Iron isomaltoside 1000

Verdict:	
Formulary inclusion:	Approved by APC for inclusion in NSJF
Formulary category:	Red
Restrictions:	As per UHNM prescribing policy
Reason for inclusion:	The Committee was satisfied with the evidence for efficacy and safety, dosing convenience, cost implications and intended place in therapy
Link to formulary:	Primary care: http://www.northstaffordshirejointformulary.nhs.uk/ Secondary care: http://uhns/clinicians/clinical-guidance/clinical-guidelines/prescribing-formularies/
Link to medicine review summary:	Primary care: https://www.stokeccg.nhs.uk/stoke-governance/policies/medicines-optimisation/formulary-review-and-verdict-sheets Secondary care: Trust Intranet→ Clinicians→ Support services → Pharmacy → Joint Formulary Related Documentation → North Staffordshire & Stoke-on-Trent Area Prescribing Committee Medicine Review Summary Verdict Sheets
Link to full review:	Primary care: https://www.stokeccg.nhs.uk/stoke-governance/policies/medicines-optimisation/formulary-review-and-verdict-sheets Secondary care: Trust Intranet→ Clinicians → Support Services → Pharmacy → Joint Formulary Related Documentation → New Medicine Committee (NMC) Medicines Reviews

Review summary:

Formulary application: MonoFer® (iron isomaltoside) is proposed for inclusion in the North Staffordshire Joint Formulary (NSJF) to replace CosmoFer® (iron dextran) and Ferinject® (ferric carboxymaltose) as the first line IV iron preparation, excluding the following patients.

- Chronic renal failure
- Dialysis
- Heart failure patients with reduced ejection fraction (where ferritin < 100 ug/L or ferritin 100-300 ug/L but transferrin saturation (TSAT) < 20%)

Dr Jane Graham (Consultant Haematologist, UHNM) submitted the application. Dr Graham and Dr Veera Gudimetla (Consultant Anaesthetist and Clinical Lead for PreAMS, UHNM) presented the application to the New Medicines Committee on 3rd April 2019. The application is also supported by the following UHNM clinicians

- Dr Kamaraj Karunanithi (Clinical director and consultant Haematologist).
- Dr Paul Ferguson (Consultant Haematologist)
- Dr Charles Baker (Clinical Director Anaesthesia, Intensive Care and Theatres)
- Mr Richard Todd (Clinical Director Obstetrics & Gynaecology)
- Dr Anthony Cadwgan (Clinical Director Specialised Medicine)
- Mrs Christine Hall (Clinical Director for General Surgery)
- Sister Sharon Wallis (Head of Midwifery/ Lead nurse for gynaecology).

Dr Graham proposes that MonoFer® replaces CosmoFer® as 1st line parental iron preparation for inpatients

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(excluding renal and heart failure patients). The reasons she and supporting clinicians are proposing changing the first line parental iron preparation to Monofer® are listed below:

- CosmoFer® dose calculation is more complicated compared to using the simplified table associated with MonoFer®. Introducing Monofer® may reduce number of prescribing errors and delays to administration associated with parental iron preparations.
- CosmoFer® is infused over 4-6 hours versus 15-30 minutes for MonoFer®. Using Monofer® instead will release nursing time and reduce length of inpatient admission.
- Clinicians are concerned that significant numbers of Ferinject® patients who require > 1000mg are being under-dosed due to lack of administration slots within the Cancer Centre, Renal Unit, AEC and lack of time/space pre-operatively. As the whole cumulative dose of Monofer® can be administered in one administration, provided it does not exceed 20mg/kg, clinicians predict that rates of under dosing will reduce if Monofer® replaces Ferinject® on the NSJF.
- Improved patient experience due to reduced infusion times/ number of hospital visits for infusions
- A test dose is required when using CosmoFer®. Monofer® does not need a test dose.
- Based on current expenditure for Ferinject® and CosmoFer®, replacing IV parental usage for all patients excluding renal and heart failure patients with MonoFer® will have minimal effect on drug expenditure

Dr Veera Gudimetla has personal positive experience of using MonoFer® in Leighton hospital, where it is included in the hospital formulary.

Licensed indications:

MonoFer® is indicated for the treatment of iron deficiency in the following conditions:

- When oral iron preparations are ineffective or cannot be used
- Where there is a clinical need to deliver iron rapidly

In practice, diagnosis of iron deficiency is based on laboratory tests

Dosing:

There are two methods available for calculating dose, as per the SPC.

Method 1: Ganzoni formula

Iron need (mg) = Body weight (kg) x (Target Hb (g/dL) – Actual Hb (g/dL)) x 2.4 + iron for iron stores (mg)

It is recommended to use the patient's ideal body weight for obese patients, and pre-pregnancy weight for pregnant women. For a person with a body weight above 35 kg, the iron stores are 500 mg. Default Hb target is 150 g/L in the Ganzoni formula. In special cases such as pregnancy consider using a lower haemoglobin target.

Method 2: Simplified table

Hb (g/L)	Patients with bodyweight 50 kg to <70 kg	Patients with body weight ≥70 kg
≥100	1000 mg	1500 mg
<100	1500 mg	2000 mg

*Maximum single dose 20mg/kg

It is recommended to use the Ganzoni formula in patients who are likely to require individually adjusted dosing such as patients with anorexia nervosa, cachexia, obesity, pregnancy or anaemia due to bleeding. The treatment effect should be monitored by blood tests.

In practice, Dr Graham intends to use method 2 for dose calculations (the simplified table), unless the patient is obese, very underweight or has anaemia due to bleeding. If BMI is >30, Dr Graham proposes ideal body weight dosing should be used according to the simplified table. Obstetric patients would be dosed according to their booking weight. If obstetric patients' booking in weight was very under or over-weight, the Ganzoni formula would be employed.

Administration

Like all parenteral irons, MonoFer® should only be administered when staff trained to evaluate and manage anaphylactic reactions is immediately available, in an environment where full resuscitation facilities can be assured. The patients should be observed for adverse effects for at least 30 minutes following each MonoFer® injection (as per other parenteral irons).

Patients should also be monitored carefully for signs and symptoms of hypersensitivity reactions. Each IV iron administration is associated with a risk of a hypersensitivity reaction. Hypersensitivity reactions can occur with all IV iron preparations, so the number of IV iron administrations should be kept to a minimum where ever possible.

Intravenous bolus injection

MonoFer® may be administered as an intravenous bolus injection up to 500 mg up to three times a week at an administration rate of up to 250 mg iron/minute. It may be administered undiluted or diluted in maximum 20 ml sterile 0.9% sodium chloride.

Intravenous drip infusion

The cumulative iron dose required may be administered in a single MonoFer® infusion up to 20 mg iron/kg body weight or as weekly infusions until the cumulative iron dose has been administered.

If the cumulative iron dose exceeds 20 mg iron/kg body weight, the dose must be split in two administrations with an interval of at least one week. It is recommended whenever possible to give 20 mg iron/kg body weight in the first administration. Dependent on clinical judgement the second administration could await follow-up laboratory tests.

Doses up to 1000 mg must be administered over more than 15 minutes. Doses exceeding 1000 mg must be administered over 30 minutes or more.

MonoFer® should be added to maximum 500 ml sterile 0.9% sodium chloride.

Dr Graham and the supporting consultants intend for MonoFer® to be administered as an intravenous drip infusion, as < 20mg/kg over 30 minutes. Rarely a second dose would be required, which would be delayed until laboratory assessment of efficacy at 4 weeks.

Injection into dialyser

MonoFer® may be administered during a haemodialysis session directly into the venous limb of the dialyser under

the same procedures as outlined for intravenous bolus injection.

Related guidance:

NICE:

NICE guideline NG24 (November 2015) includes recommendations on alternatives to transfusion, individual component transfusion, patient safety and patient information. Section 1.1.3 states intravenous iron should be considered before or after surgery for patients who:

- have iron-deficiency anaemia and cannot tolerate or absorb oral iron, or are unable to adhere to oral iron treatment
- are diagnosed with functional iron deficiency
- are diagnosed with iron-deficiency anaemia, and the interval between the diagnosis of anaemia and surgery is predicted to be too short for oral iron to be effective

Using alternatives to transfusion at the time of surgery is one way of reducing transfusion-related risk and transfusion-related costs.
NICE blood transfusion quality standard 138 (QS138 - December 2016) requires 'people with iron-deficiency anaemia who are having surgery are offered iron supplementation before and after surgery'.

SMC:
MonoFer® use is restricted to administration by high dose infusion within the licensed indication but excluding use in patients receiving haemodialysis. The manufacturer's economic case did not consider the cost-effectiveness of IV bolus administration or use in haemodialysis patients. Efficacy data are limited to two small open-label non comparative studies in patients with chronic kidney disease and chronic heart failure. Haemoglobin levels significantly increased from baseline in one study only.

RDTC: No published guidance available

MTRAC: No published guidance available

AWMSG : No published guidance available

Background information:

Iron deficiency anaemia (IDA) results from diminished red blood cell/haemoglobin production due to inadequate iron stores in the body, or inability to effectively utilise iron. Initial treatment for IDA is oral iron preparations, however oral iron preparations are associated with poor absorption, poor compliance, adverse reactions and treatment discontinuation. Parenteral iron administration bypasses issues of absorption, compliance and GI toxicity and offers a rapid and efficient means of iron correction. Parenteral iron is indicated for the treatment of iron deficiency where oral iron is ineffective/cannot be used, or where there is a clinical need to deliver iron rapidly.

Currently three parenteral iron preparations are included in the NSJF: Venofer® (iron sucrose), CosmoFer® and Ferinject®.

- Venofer® is prescribed for haemodialysis patients requiring maintenance iron replacement
- Ferinject® is restricted to the following cohorts; Gastroenterology and Haematology outpatients, Day case patients eg AEC ward and Renal patients

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- CosmoFer® is prescribed for other adult inpatients who do not fall into the above cohorts

A previous application form for MonoFer® was submitted and reviewed by the Area Prescribing Committee in March 2012. At that time the committee concluded there was insufficient evidence regarding the efficacy and safety of MonoFer® compared to Ferrinject®, adverse effects listed in Monofer®'s SPC were based on those for other iron parental preparations and doses could only be calculated using the Galzoni formula. The NMC and APC also stated a lack of clinical experience with MonoFer® within UHNM was a factor contributing to their decision.

Since 2012, clinical trials have been published demonstrating efficacy of MonoFer® to improve markers of iron deficiency anaemia in patients receiving dialysis, non-dialysis-dependent chronic kidney disease, chronic heart failure (CHF), inflammatory bowel disease (IBD), underlying cancer, cardiac surgery and postpartum haemorrhage. The safety and efficacy of MonoFer® has been compared to Venofer®; where MonoFer® was demonstrated as being more effective in achieving a rapid improvement in haemoglobin. There are no direct comparative trials between CosmoFer® or Ferinject®. From a safety perspective, there is now adverse effects data based on post-marketing data for MonoFer®, demonstrating similar side effect profile to Ferinject® and CosmoFer®
MonoFer® doses can now be calculated using a simplified dosing table for the vast majority of patients, therefore allowing dose banding in a similar style to Ferinject®. With MonoFer®, a total dose iron infusion <20mg/kg can be administered in 30 minutes in contrast to Ferinject® (where the maximum cumulative dose per week is 1000mg) regardless of body weight. This reduces the number of hospital visits required and reduces exposure to iron infusions.

Clinicians are concerned that significant numbers of Ferinject® patients who require > 1000mg are being under-dosed due to lack of administration slots within the Cancer Centre, Renal Unit, AEC and lack of time/space pre-operatively. As the whole cumulative dose of Monofer® can be administered in one administration, provided it does not exceed 20mg/kg, clinicians predict that rates of under dosing will reduce if Monofer® replaces Ferinject® on the NSJF.

Efficacy:
International consensus statements on the management of pre-operative anaemia (Munoz 2017) state sufficient data exist to support intravenous iron as efficacious and safe. Intravenous iron should be used as front-line therapy in patients who do not respond to oral iron or are not able to tolerate it, or if surgery is planned for < 6 weeks after the diagnosis of iron deficiency.

International consensus statements on the management of post-operative anaemia (Munoz 2018) recommends early intravenous iron therapy after considering contraindications, ideally administered using a single high-dose preparation for the repletion of iron stores. The authors highlight that NICE recommends offering oral iron after surgery to patients with iron deficiency anaemia, however, in the postoperative period, oral iron is often not tolerated and/or absorbed, and results in poor treatment adherence. In addition, the inflammatory response induced by surgery stimulates hepcidin synthesis and release, which in turn inhibits intestinal iron absorption, making oral iron therapy largely ineffective. Randomised placebo-controlled trials (RCT) in orthopaedic and cardiac surgery patients have demonstrated that oral iron therapy was not better than placebo in correcting postoperative anaemia and reducing transfusion requirements; thus patients presenting with postoperative iron deficiency and/or moderate-to-severe postoperative anaemia (haemoglobin < 100 g.l_1) may benefit from IV iron supplementation, which has proven to be more effective than oral iron in a number of surgical settings.

Several clinical trials have demonstrated the efficacy of MonoFer® to safely improve markers of iron deficiency anaemia. These have been conducted in patients receiving dialysis, non-dialysis-dependent chronic kidney disease (NDD-CKD), chronic heart failure (CHF), inflammatory bowel disease (IBD), underlying cancer, those undergoing

cardiac surgery and postpartum haemorrhage.

Chronic Kidney Disease

Wikstrom et al investigated in patients with NDD-CKD or those with stage 5 CKD who were either iron naïve or were prepared to switch from their usual IV iron therapy. The primary endpoint was to establish the safety profile of MonoFer® in CKD patients. The secondary endpoint was to establish the efficacy of MonoFer®. 584 treatments were given (523 IV bolus 100mg, 17 IV bolus 100-200mg and 44 high-dose infusions) with single doses up to 1800mg. Haemoglobin, transferritin saturation and ferritin significantly increased. Additionally, no acute hypersensitivity or delayed allergic reactions were reported. The study concluded that MonoFer® with repeated IV bolus injections or single high-dose infusions was well tolerated and improved markers of anaemia.

(Kalra et al), the primary objective was to compare MonoFer® to oral iron sulphate in reducing renal-related anaemia, evaluated as the ability to increase Hb. It was concluded that MonoFer® was more efficacious than oral iron in increasing Hb and proved to be better tolerated than oral iron at the tested dose levels in NDD-CKD patients.

Leistikow et al presented an observational study investigating the treatment routine, efficacy, safety, and tolerability of MonoFer® in CKD patients. 525 patients were concomitantly treated with erythropoiesis stimulating agents, but the proportion significantly reduced with MonoFer® administration. This study concluded that MonoFer® is a cost effective IV iron therapy and can reduce the requirements for erythropoiesis stimulating agents.

Inflammatory Bowel Disease

Reinisch et al evaluated the efficacy of MonoFer® versus oral iron in reducing iron deficiency anaemia, evaluated as the ability to increase Hb at week 8 in patients with IBD and iron deficiency anaemia. The mean infusion dose was 885mg and mean bolus dose was 883mg. The authors of this study state that using the Ganzoni formula led to an underestimation of iron requirements. In previous trials, the mean cumulative dose has been higher, where doses up to 3600mg have been required. This IBS trial was extended for 1 year to evaluate the need for additional MonoFer® doses. In patients with an Hb ≥ 12.0g/dL at baseline, 74% were able to maintain their Hb ≥ 12.0g/dL during the 1 year.

Dahlerup and Lindgren presented a prospective, open-label, multicentre trial conducted in 21 patients with IBD and iron deficiency anaemia. The authors concluded that infusions of high-dose MonoFer®, administered as single doses of up to 2,000 mg and cumulative doses of up to 3,000 mg over a short duration, were completed without safety concerns and were efficacious in increasing Hb levels in patients with IBD.

Cancer patients with anaemia

Birgegård et al presented an open-label randomized clinical trial in anaemic cancer patients which compared the efficacy of MonoFer® to oral iron sulphate, determined as change in Hb from baseline to week 4. MonoFer® was demonstrated as being non-inferior to oral iron sulphate in its ability to increase haemoglobin. Both resulted in comparable sustained increases in haemoglobin over time; although oral iron was associated with more adverse effects.

Patients undergoing cardiac surgery

Johansson et al compared MonoFer® to placebo in the ability to change Hb from baseline to 4 weeks in patients undergoing elective or sub-acute coronary artery bypass graft, valve replacement, or a combination thereof. This study concluded that MonoFer® can be used safely and effectively to prevent anaemia after cardiac surgery.

Chronic Heart Failure

Hildebrandt et al investigated the safety profile of a high, single dose of MonoFer® in a small group of patients with CHF, and secondary endpoints included effects on relevant haematology parameters and quality of life. Overall, haemoglobin, iron parameter and quality of life improved. Additionally, no adverse effects were reported and no acute or delayed hypersensitivity reactions were observed.

Comparison to Venofer®

An open-label, randomised clinical trial compared the safety and efficacy of MonoFer® to Venofer® in patients with IDA with various clinical conditions (Derman R. et al). This was a multicentre, comparative trial over a 5 week period. Patients were randomised 2:1 to either MonoFer® (cumulative dose 1000mg, 1500mg or 2000mg) or Venofer®. For patients randomised to MonoFer® 1500mg or 2000mg, the doses were split and the second dose administered after a one week interval. The MonoFer®dose was calculated based on haemoglobin level and body weight, whereas the Venofer® dose was calculated using the Ganzoni formula. The primary efficacy endpoint was the proportion of patients with an Hb increase of ≥2 g/dL from baseline at any time from weeks 1 to 5. The secondary efficacy endpoints included time to Hb increase ≥2 g/dL. For all biochemical efficacy parameters, greater improvements were found with MonoFer®. MonoFer® was more effective than Venofer® in achieving a rapid improvement in haemoglobin. Serious adverse reactions were reported equally by 0.6% of patients in both groups. Furthermore, MonoFer® has an advantage of allowing higher cumulative dosing in fewer administrations.

Comparison to other parenteral iron preparations

There are no direct comparative trials with CosmoFer® or with Ferinject

Pollock and Muduma developed a budget impact model to evaluate the cost of using MonoFer® to Ferinject®, CosmoFer® and Venofer® in patients with iron deficiency anaemia. To establish iron need, iron deficits were modelled using a simplified dosing table. The base case analysis was conducted over 1 year in patients with iron deficiency anaemia with mean bodyweight of 82.4 kg and haemoglobin levels of 9.99 g/dL. Costs were modelled using UK health care resource groups. Using MonoFer® or CosmoFer® in place of Ferinject® and Venofer® resulted in a marked reduction in the number of infusions required to correct iron deficits. Patients administered with MonoFer® required multiple infusions in 35% of cases, compared with 35%, 77% and 100% of patients with CosmoFer®, Ferinject® and Venofer®, respectively. Total costs were estimated to be £451.00 per patient with MonoFer® or CosmoFer®, relative to £594.00 with Ferinject®. Savings with MonoFer® would be £143.00 (24%). Additionally, for care providers, the shorter infusion time with MonoFer® would allow greater savings compared to CosmoFer®. The cost analysis for the health economy is discussed below.

Safety:

Warnings and precautions

The precautions and contraindications listed are similar to other parenteral iron preparations.

Hypersensitivity

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The administration of parenteral iron preparations is associated with hypersensitivity reactions. This risk is enhanced for patients with known allergies including drug allergies, including patients with a history of severe asthma, eczema or other atopic allergy. There is also an increased risk of hypersensitivity reactions to parenteral iron complexes in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis).

Facilities for cardio respiratory resuscitation and equipment for handling acute anaphylactic reactions should be available, including an injectable 1:1000 adrenaline solution. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate. A test dose for Monofer® is no longer recommended, as data suggests that an allergic reaction can still occur in patients who have not reacted to a test dose, however CosmoFer® administration still requires a 25mg test dose. All intravenous iron preparations should be used with caution, even if previous administrations have been well tolerated.

Compensated liver dysfunction

Parenteral iron should only be administered after careful benefit/risk assessment. Parenteral iron administration should be avoided in patients with hepatic dysfunction (alanine aminotransferase and/or aspartate aminotransferase > 3 times upper limit of normal) where iron overload is a precipitating factor, in particular Porphyria Cutanea Tarda (PCT). Careful monitoring of iron status is recommended to avoid iron overload

MonoFer® (and other parenteral irons) should not be used in patients with ongoing bacteraemia and should be used with caution in acute or chronic infection. Paravenous leakage of MonoFer® at the injection site may lead to irritation of the skin and potentially long lasting brown discolouration at the site of injection. In case of paravenous leakage, the administration of MonoFer® must be stopped immediately.

Intravenous iron products should not be used during pregnancy unless clearly necessary. Treatment should be confined to the second or third trimester, provided the benefits of treatment clearly outweigh the potential serious risks to the foetus such as anoxia and foetal distress.

Contraindications

MonoFer® is contraindicated in the following group of patients:

- Hypersensitivity to the active substance or any of its excipients
- Known serious hypersensitivity to other parenteral iron products
- Non-iron deficiency anaemia (e.g. haemolytic anaemia)
- Iron overload or disturbances in utilisation of iron (e.g. haemochromatosis, haemosiderosis)
- Decompensated liver disease

Drug interactions

The absorption of oral iron is reduced when administered concomitantly with parenteral iron preparations; consequently, oral iron therapy should not be started earlier than 5 days after the last injection of MonoFer®. Additionally, parenteral iron may cause falsely elevated values of serum bilirubin and falsely decreased values of serum calcium. This is similar to other parental iron preparations.

Place in therapy:
MonoFer® (iron isomaltoside) is proposed for inclusion in the North Staffordshire Joint Formulary (NSJF) to replace CosmoFer® (iron dextran) and Ferinject® (ferric carboxymaltose) as the first line IV iron preparation, excluding the following cohorts

Author: Xin Wei Tan, Secondary/Primary Care Interface Pharmacist, UHNM Date approved by APC: xx/xx/xx

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- Chronic renal failure
- Dialysis
- Heart failure patients with reduced ejection fraction (where ferritin < 100 ug/L or ferritin 100-300 ug/L but transferrin saturation (TSAT) < 20%)

Cost:

Based on current expenditure for Ferinject® and CosmoFer®, replacing IV parental usage for all patients excluding renal and heart failure patients with MonoFer® will have minimal effect on drug expenditure, despite MonoFer® being more expensive per gram compared to CosmoFer®. This is because the majority of drug expenditure for IV parental preparations is for Ferinject®, which is now slightly more expensive compared to MonoFer®. This excludes the cost savings to the health economy through reduced admissions/length of stay, reduced blood component usage and more efficient use of staff time.

Total drug expenditure of CosmoFer® and Ferinject® from February 2018 – January 2019 (excluding Venofer® for renal patients)	£453,485.31 (£16,622.23 due to CosmoFer®, £436,863.07 due to Ferinject®)
Predicted drug expenditure for MonoFer® (1g and 500mg vials) if all CosmoFer® and Ferinject® usage replaced	£453,460.08

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