Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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Resubmission

ferric carboxymaltose 50mg iron/mL solution for injection/infusion (Ferinject®) SMC No. (463/08)
Vifor Pharma UK Ltd

06 May 2011

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 second resubmission

ferric carboxymaltose (Ferinject®) is accepted for restricted use within NHS Scotland.

Indication under review: the treatment of iron deficiency when oral iron preparations are ineffective or cannot be used. The diagnosis must be based on laboratory tests.

SMC restriction: use is restricted to administration by intravenous 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.

Ferric carboxymaltose was superior to oral ferrous sulphate in raising haemoglobin levels in non-dialysis-dependent patients with chronic kidney disease and iron deficiency anaemia.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

The treatment of iron deficiency when oral iron preparations are ineffective or cannot be used. The diagnosis must be based on laboratory tests.

Dosing Information

(Note dosing information relating to haemodialysis is not relevant to the SMC restriction)
The adequate cumulative dose must be calculated, using a formula provided, for each patient individually and must not be exceeded.

It must be administered by the intravenous (iv) route only:

- by bolus injection, during a haemodialysis session undiluted directly into the venous limb of the dialyser, or by drip infusion;
- by intravenous bolus injection up to a maximum single dose of 200mg of iron per day, not more than three times a week;
- by intravenous infusion, up to a maximum single dose of 1,000mg of iron but not exceeding 15mg per kg body weight or the calculated cumulative dose. 1,000mg of iron must not be administered as an infusion more than once a week. The minimum administration time is 15 minutes for doses of ≥ 500mg.

Product availability date

June 2008

Summary of evidence on comparative efficacy

Ferric carboxymaltose is a Type I polynuclear iron (III)-hydroxide carbohydrate complex developed as a parenteral iron replacement therapy. The company has requested that SMC consider the use of ferric carboxymaltose only for the treatment of iron deficiency anaemia in non-dialysis-dependent patients with chronic kidney disease (CKD).

Two comparative studies were described: one versus oral ferrous sulphate in the target population of non-dialysis-dependent patients with CKD and one versus iv iron sucrose in a haemodialysed population. Although this latter study is not in the target population, brief details are presented as this is the only comparative study with another parenteral iron formulation.

Evidence for the efficacy of ferric carboxymaltose in non-dialysis-dependent patients with CKD who require iron supplementation came from a randomised, open-label, active-controlled study and its open-label, non-randomised extension phase. Patients aged 12 or over with a glomerular filtration rate (GFR) ≤ 45 mL/min/1.73m^2 and with an average haemoglobin (Hb) level ≤ 11g/dL were enrolled. There was a screening period, by the end of which patients were required to have a transferrin saturation (TSAT) ≤ 25% and ferritin level ≤ 300 microgram/L, not have had parenteral iron for 12 weeks and (if on epoetin) have been on a stable epoetin (EPO) dose for 8 weeks. Stratification was by degree of CKD and by baseline Hb within current use of EPO.

Two hundred and fifty patients were randomised to receive either iv ferric carboxymaltose up to a maximum of 1,000mg (15mg/kg if weight ≤ 66kg) on Day 0, then to a maximum of 500mg (again 15mg/kg if weight ≤66kg) around Day 14 and again around Day 28 (taking into account TSAT and ferritin levels) or oral ferrous sulphate 325mg three times daily for 56 days. The EPO dose remained unchanged although could be decreased, for safety reasons only, at the investigator's discretion. The primary efficacy endpoint was the percentage of patients achieving an increase in their Hb concentration of ≥ 1g/dL at any time between baseline and the end of the study or the time of intervention (change in EPO dose, other use of iron or blood transfusion). This was determined in the modified intention-to-treat (mITT) population, which comprised those who received at least one dose of study drug, had a stable EPO dose for at least 8 weeks prior to randomisation and had at least one post-baseline Hb measurement; comparison between the ferric carboxymaltose and ferrous sulphate groups was with Fisher's exact test.

In the mITT population (n=245), the primary endpoint was achieved in significantly more of the ferric carboxymaltose group, 60% (87/144) than the ferrous sulphate group, 35% (35/101), demonstrating the superiority of ferric carboxymaltose. The majority of patients in both groups were not using EPO at randomisation (ferric carboxymaltose 76% and ferrous sulphate 75%). For those not using EPO, the success rate was 53% in the ferric carboxymaltose group and 30% in the ferrous sulphate group; in those using EPO, success was achieved in 85% of ferric carboxymaltose patients and 50% of ferrous sulphate patients.

Patients could enter an open-label, non-randomised 44 week extension study in which all patients received ferric carboxymaltose iv 15mg/kg up to a maximum of 1,000mg or 500mg or no dose, dependent on TSAT and ferritin values. The efficacy population comprised 140 patients. There was no primary efficacy endpoint, but secondary endpoints included the percentage of patients with clinical success (defined as Hb level ≥11 g/dL, TSAT 30 to 50% and ferritin 100 to 800microgram/L) achieved at least once. Patients who had significant changes in their EPO dosing during the study were excluded from analyses with Hb as an outcome.

Most patients (59%) in this study had received ferric carboxymaltose in the original study and mean baseline Hb level was 10.4g/dL. Clinical success was achieved in 51% of patients and 10% achieved sustained clinical success (clinical success at more than half the assessments).

A randomised, open-label study in 240 haemodialysed patients with iron deficiency anaemia, which differs from the target population of non-dialysis-dependent patients, compared iv ferric carboxymaltose with iv iron sucrose, both at doses of 200mg two or three times weekly until their individually calculated required cumulative dose had been reached. The percentage of patients achieving an increase in Hb of ≥1g/dL at 4 weeks was 46% (45/97) in the ferric carboxymaltose group compared with 37% (32/86) in the iron sucrose group. Sixty-one percent of the ferric carboxymaltose patients and 62% of the iron sucrose patients were receiving EPO during the study.

Summary of evidence on comparative safety

In the comparison with oral iron, significantly fewer patients in the ferric carboxymaltose group experienced at least one treatment-emergent adverse event (AE) compared with those in the ferrous sulphate group (44% versus 59%). Significantly fewer patients in the ferric carboxymaltose group (2.7%) experienced at least one drug-related AE compared with the ferrous sulphate group (26%).

Serious AEs were reported by 8.8% of the ferric carboxymaltose patients and 9.7% of the ferrous sulphate patients. Premature discontinuations due to AEs occurred in 3.4% of the ferric carboxymaltose group and 6.8% of the ferrous sulphate group.

When compared with oral ferrous sulphate, those receiving ferric carboxymaltose experienced significantly less constipation (1.4% versus 18%). More patients in the ferrous sulphate group reported nausea, diarrhoea, discoloured faeces and gastrointestinal haemorrhage, whereas more patients in the ferric carboxymaltose group reported peripheral oedema, hyperkalaemia, hypotension and urinary tract infections.

In the study in the non-target population of haemodialysed patients, 43% of ferric carboxymaltose and 40% of iron sucrose patients experienced at least one treatment emergent adverse event, with 4% in each group experiencing severe events. Overall there was no difference in the safety profile between the two treatment groups.

Summary of clinical effectiveness issues

Ferric carboxymaltose is licensed for the treatment of iron deficiency when oral preparations are ineffective or cannot be used. The target population proposed by the company is non-dialysis-dependent patients with CKD, however no comparative studies versus other iv iron preparations have been conducted in this patient group. Comparative data with parenteral preparations are limited to patients on haemodialysis and the study versus iron sucrose was not powered to detect treatment differences.

The pivotal study compared ferric carboxymaltose with oral ferrous sulphate treatment therefore does not reflect the patient group covered by the marketing authorisation for ferric carboxymaltose which excludes patients who can receive oral iron therapy.

Current iv iron treatment options are iron sucrose, iron dextran and iron isomaltoside 1000. Iron sucrose can be administered by slow iv injection or infusion, and the total single dose cannot exceed 200mg of iron, given not more than three times a week. Iron dextran can be administered by slow iv injection or infusion, at a dose of up to 200mg up to three times weekly, or as a total dose infusion of up to 20mg/kg given over 4 to 6 hours. Iron isomaltoside may be administered as a 100 to 200mg iv bolus injection up to three times a week or as a total dose infusion of up to 20mg iron/kg body weight.

Potential advantages of ferric carboxymaltose, and also of iron isomaltoside 1000, compared with other iv iron products are that high dose infusions can be administered over a relatively short period of time (≥15 minutes for ferric carboxymaltose and 60 minutes for iron isomaltoside)

and test doses are not required. However, with both preparations repeat dosing may still be needed for patients requiring large cumulative doses of iron.

The option to give a single, rapidly administered dose of iron has the potential to reduce duration and frequency of out-patient clinic visits. Clinical experts indicate that most pre-dialysis patients are able to receive oral therapy, suggesting that the number of patients eligible for parenteral iron is small. Clinical experts suggested use of ferric carboxymaltose may be appropriate in peritoneal dialysis patients in some circumstances.

There are insufficient data to compare the relative risks of hypersensitivity reactions with iv iron products. The economic case is based on the study in haemodialysis patients described above, a group excluded from the target population proposed by the submitting company.

Summary of comparative health economic evidence

The manufacturer presented a cost-minimisation analysis comparing ferric carboxymaltose with iron sucrose in non-dialysis-dependent patients. The time period was the duration of a course of treatment. The evidence base supporting equivalent outcomes for the two treatments, as necessary for a cost-minimisation analysis, was based on assumption only, rather than by using directly comparative trial evidence or a formal indirect comparison. Costs in the model related to the cost of the drugs, consumables, nursing time to administer the drug, and the NHS cost of patient transport services. It was assumed 32% of patients require NHS transport and that the average distance was 40 miles each way (higher in more rural areas, lower in cities).

Assuming Agenda for Change band 6 nursing input costed according to SMC guidance and 32% of patients requiring NHS transport services, the manufacturer estimated that an equivalent dose of ferric carboxymaltose given as a single 15 minute infusion (in the context of a 30-minute appointment) would be associated with cost savings. These equated to £7.39 less per course than iron sucrose 600mg given as 3 x 200mg bolus injections, each within a 30-minute appointment (£146.25 per patient versus £153.64).

A survey of Scottish centres carried out by the manufacturer suggested 775mg of iron sucrose was the average dose used in practice and this would require a fourth injection (and appointment). The savings in this case would be £19.52 compared with iron sucrose 800mg given as 4 x 200mg bolus injections, each within a 30- minute appointment (£184.44 versus £203.96).

In a sensitivity analysis, ferric carboxymaltose was cost saving in the base case so long as 24% or more of patients require NHS transport; if use is less than this then iron sucrose becomes progressively less expensive.

The main limitation with the analysis was that the clinical equivalence of different treatments was assumed rather than proven. Despite this, the economic case was considered demonstrated.

Summary of patient and public involvement

A Patient Interest Group submission was received from:

- The National Kidney Federation

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline 103, "Diagnosis and management of chronic kidney disease" in 2008. Within discussions about the anaemia of chronic kidney disease, the use of supplemental iron is not mentioned, with advice being "Erythropoiesis stimulating agents should be considered in all patients with anaemia of chronic kidney disease to improve their quality of life".

The National Institute for Health and Clinical Excellence (NICE) published "Anaemia management in chronic kidney disease, Clinical Guideline 114" in February 2011. It noted that "The available published evidence does not suggest the most effective and safest dose, frequency, preparation or route of administration of iron in anaemia of chronic kidney disease patients with functional iron deficiency prior to erythropoiesis stimulating agent therapy. Guideline Development Group (GDG) consensus was that patients with anaemia associated with chronic kidney disease and functional iron deficiency will require intravenous iron treatment. The published evidence did not allow the GDG to recommend a preparation. At this time "Two preparations are available in the UK and the dose and frequency will be dictated by the preparation used and by measurement and monitoring of iron indices (serum ferritin and % hypochromic red cells or % transferrin saturation)." This advice pre-dates licensing of ferric carboxymaltose and iron isomaltoside.

The Renal Association and Royal College of Physicians of London produced "Chronic kidney disease in adults: UK guidelines for identification, management and referral" in 2006. For stages 3 and 4-5 CKD, this recommended the treatment of anaemia with iv iron, with or without erythropoiesis stimulating agents, after the exclusion of other causes of anaemia.

In a Clinical Practice Guideline published in November 2010 entitled "Anaemia of CKD", the UK Renal Association recommended "oral iron will, in general, be sufficient to attain and maintain the haemoglobin above targets in erythropoiesis stimulating agent treated chronic kidney disease patients not yet requiring dialysis and in those on peritoneal dialysis. In contrast most haemodialysis patients will require intravenous iron."

Additional information: comparators

Comparators are other parenteral preparations, iron sucrose, iron dextran and the recently licensed iron isomaltoside 1000 that is currently going through the SMC assessment process.

The total dose of iron required will be entirely determined by the individual patient's clinical need. For parenteral preparations, this is based on haemoglobin levels and weight. Each of these preparations can be given as a 200mg dose up to three times weekly so this is the means of comparison. The costs of maximal total dose infusions are also included.

Cost of relevant comparators

Drug	Bolus dose regimen	Cost per week(£)
Ferric carboxymaltose	**200mg intravenously three times per week**	**115**
Iron isomaltoside	200mg intravenously three times per week	102
Iron sucrose	200mg intravenously three times per week	56
Iron dextran	200mg intravenously three times per week	48
Drug	**Total dose infusion regimen**	**Cost of 1,000mg dose (£)**
Ferric carboxymaltose*	**15mg iron/kg body weight iv infusion**	**191**
Iron isomaltoside 1000	15 to 20mg iron/kg body weight iv infusion	170 to 237
Iron dextran	15 to 20mg iron/kg body weight iv infusion	80 to 112

Doses are for general comparison and do not imply therapeutic equivalence. Cost of iron dextran from eVadis on 2 March 2011. Cost of iron sucrose and iron isomaltoside from Monthly Index of Medical Specialities February 2010. Cost of ferric carboxymaltose from submitting company. Total dose infusion (TDI) regimen based on 70kg body weight (dose range 1,000mg to 1,400mg). * NB Maximum TDI dose for ferric carboxymaltose is 15mg iron/kg body weight (1,000mg).

Additional information: budget impact

The manufacturer estimated that if patients receiving iv iron sucrose and iron dextran were to receive ferric carboxymaltose instead then from an NHS budget perspective there would be a saving of £1k in year one rising to £10k in year five. The manufacturer did not supply an estimate confined to the medicines budget only. However the manufacturer did present figures to show that the net incremental drug cost of ferric carboxymaltose compared to iron sucrose at a therapeutic dose of iv iron of 600mg was £58.50. . On the basis of the patient numbers the manufacturer has assumed, this would imply a net medicines budget of £9k in year one rising to £81k in year five.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission.

Qunibi WY, Martinez C, Smith M, et al. Efficacy and Safety of IV Ferric Carboxymaltose (FCM) Compared to Oral Iron in Anemic Patients with Non-Dialysis-Dependent CKD. 45th Congress of the European Renal Association and the European Dialysis and Transplant Association. Stockholm, 2008 (Abstract plus poster MO018).

Vifor Pharmaceuticals. Data on file: Clinical Study Report 1VIT04004. Comparison of the safety and efficacy of a unique intravenous iron preparation (VIT-45) versus oral iron in the treatment of anemia in non-dialysis dependent chronic kidney disease, 2007.

Vifor Pharmaceuticals. Data on file: Clinical Study Report 1VIT05005. Open label extension study evaluating the long term safety, tolerability and efficacy of an iron maintenance dosing strategy utilizing intravenous VIT-45 in the treatment of anemia in non-dialysis dependent (NDD) chronic kidney disease (CKD), 2007.

Vifor Pharmaceuticals. Data on file: Clinical Study Report VIT-IV-CL-015. A multicentre, controlled Phase III Study to Compare the Efficacy and Safety of VIT-45 and Venofer in the Treatment of Iron Deficiency Anaemia Associated with Chronic Renal Failure in Patients on Haemodialysis, 2005.

**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/*

This assessment is based on data submitted by the applicant company up to and including **15 April 2011.**

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. 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.

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.