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

Vifor Pharmaceuticals

17 December 2010

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 NHS Scotland. The advice is summarised as follows:

**ADVICE: following a resubmission**

**Ferric carboxymaltose (Ferinject®)** is not recommended for 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.

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. It has also shown similar efficacy to standard intravenous iron therapy in haemodialysed patients.

However, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

**Chairman**

Scottish Medicines Consortium

Published 17 January, 2011
**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**
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.

**Product availability date**
June 2008

**Summary of evidence on comparative efficacy**

Ferric carboxymaltose (FCM) is a Type I polynuclear iron (III)-hydroxide carbohydrate complex developed as a parenteral iron replacement therapy for the treatment of iron deficiency anaemia. It has a marketing authorisation for use in the treatment of iron deficiency when oral iron preparations are ineffective or cannot be used. The manufacturer has requested that SMC consider the use of FCM only for the treatment of iron deficiency anaemia in non-dialysis-dependent (NDD) patients with chronic kidney disease (CKD).

Two comparative studies have relevance to the submission made: one versus oral ferrous sulphate in the target population of NDD patients with CKD and one versus iv iron sucrose in a haemodialysed population.

Evidence for the efficacy of FCM in NDD patients with CKD who required 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/1.73m² and with an average haemoglobin (Hb) level (from 2 results taken within a seven day period) ≤ 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 have been on a stable erythropoietin (EPO) dose for 8 weeks (if on EPO). Eligible patients were then randomised to receive either iv FCM or oral ferrous sulphate for an 8 week treatment period. Stratification was by degree of CKD (GFR ≤ 15.0, 15.1 to 30.0, and 30.1 to 45ml/min/1.73m²) and by baseline haemoglobin (10.1 to 11.0, 9.1 to 10.0 and ≤ 9.0g/dL) within current use of EPO. Two hundred
and fifty patients were randomised to receive either iv FCM 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, if relevant, 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, and was assessed for superiority of FCM with Fisher’s exact test.

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

Patients who completed this study until day 56 and those who had been discontinued because they required the addition of EPO, an EPO dose increase or the use of iron outside the protocol, were allowed to enter an open-label, non-randomised extension study. For a period of up to 44 weeks, visits were scheduled every 28 days, and all patients were to receive FCM iv 15mg/kg up to a maximum of 1,000mg or 500mg or no dose, dependent on TSAT and ferritin values. The efficacy population, who comprised those patients who received at least one dose of FCM in the original and/or extension study and had at least one assessment of clinical success after the start of the extension study, contained 140 patients. There was no primary efficacy endpoint for this study, but secondary ones included the percentage of patients with clinical success (defined as Hb level ≥11 g/dL, TSAT 30 to 50% and ferritin 100 to 800 microgram/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 FCM 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 compared iv FCM 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**

Parenterally administered iron preparations can cause allergic or anaphylactoid reactions, which may be potentially fatal.
In the comparative study, significantly fewer patients in the FCM group experienced at least one treatment-emergent adverse event (AE) compared with those in the ferrous sulphate group (44% compared with 59%). At least one drug-related AE was experienced by significantly fewer patients in the FCM group (2.7%) compared with the ferrous sulphate group (26%). Serious AEs were reported by 8.8% of the FCM patients and 9.7% of the ferrous sulphate patients. Premature discontinuations due to AEs occurred in 3.4% of the FCM group and 6.8% of the ferrous sulphate group.

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

In the study in 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. Five percent and 10% respectively experienced at least one probably drug-related adverse event. Overall there were no differences in 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 manufacturer is non-dialysis-dependent patients with CKD, however no comparative studies versus other intravenous 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.

Current intravenous iron treatment options are iron sucrose and iron dextran. Iron sucrose can be administered by slow intravenous injection or infusion, and the total single dose cannot exceed 200mg of iron, given not more than three times a week. An initial test dose is required as a precaution against allergic or anaphylactoid reactions. Iron dextran can be administered by slow intravenous 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. A test dose is required with each dose.

Unlike other intravenous iron preparations, FCM does not require a test dose to be given and can be administered in large (up to 1,000mg), rapidly administered weekly doses (15 minute infusion time). However, repeat dosing may still be needed for patients requiring large cumulative doses of FCM.

The option to give a single, rapidly administered dose of iron has the potential to reduce duration and frequency of out-patient clinic visits. 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.
Summary of comparative health economic evidence

The manufacturer presented a cost-minimisation analysis comparing ferric carboxymaltose with iron sucrose or iron dextran in non-dialysis-dependent patients. The time period was the duration of a course of treatment. The evidence base supporting equivalent outcomes for the three 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, and nursing time to administer the drug. The cost of patient transport services were also considered in a sensitivity analysis but it was not clear why this was not considered as part of the base case.

Assuming band 6 nursing input and no patients requiring transport services, the manufacturer estimated that an equivalent dose of ferric carboxymaltose given as a single 15 minute infusion would be associated with the following cost savings per course:

- £26.14 less than iron sucrose 600mg given as 3 x 30 minute infusions (£160.82 per patient versus £186.96)
- £44.96 less than iron sucrose 800mg given as 4 x 30 minute infusions (£204.32 versus £249.28),
- £63.78 less than iron sucrose 1,000mg given as 5 x 30 minute infusions (£247.82 versus £311.60), and
- £207.20 less than iron dextran 1,000mg given as a single 6 hour infusion (£247.82 versus £455.02).

The comparison with iron sucrose 600mg is likely to be the most relevant of the comparisons presented.

From the results presented, it is clear that a key driver of the results was the estimated savings in nursing time, and for each drug administration two scenarios were presented. In the scenario used to estimate the results above, a 1:1 ratio of nurse per patient for the duration of the infusion was assumed. In a second scenario, nurses were assumed to administer infusions to more than one patient at a time. Threshold analysis suggested that ferric carboxymaltose was cost-saving so long as a nurse did not supervise more than 1.5 patients on average at one time.

In practice, Scottish clinicians report patients are treated using a 10-minute bolus injection during a 30-minute appointment, and a course requires three or more weekly appointments. No cost-effectiveness evidence was presented for this scenario.

The valuation of nursing time released was based on a Band 6 nurse at £60 per hour based on a published costing source. However, this publication also reported a range of cost per hour estimates that were lower, given the exclusion of some overhead costs. While Scottish clinicians agreed that the time released would be valuable, the true value of the opportunity cost per hour may be lower than the £60 used in the base case and this could therefore affect the cost savings projected in the manufacturer’s analysis. The manufacturer provided a sensitivity analysis which showed that if nursing time were valued using salary plus on-costs alone, then a course of ferric carboxymaltose would be more expensive than iron sucrose.

The manufacturer provided some additional scenario analysis to show subgroups of patients for whom ferric carboxymaltose would be a cost-effective option. This indicated that for a subgroup of patients who require patient transport services, ferric carboxymaltose would be associated
with a saving of £48 per patient compared to iron sucrose 600mg. This estimate assumed savings in nurse time were valued at the lower rate based on salary plus on-costs alone.

Given the sensitivity of the result to the assumed value of nursing time released, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

**Summary of patient and public involvement**


**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 a document in 2006 “Anaemia management in chronic kidney disease: national clinical guideline for management in adults and children”. 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.

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 intravenous iron, with or without erythropoiesis stimulating agents, after the exclusion of other causes of anaemia.

In a draft Clinical Practice Guideline from July 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 and iron dextran.

The total dose of iron required will be entirely determined by the individual patient’s clinical need. For intravenous 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 cost of a single weekly dose of ferric carboxymaltose is also included.

Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per dose (£)</th>
<th>Cost per week (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ferric carboxymaltose *</td>
<td>200mg intravenous dose one to three times per week</td>
<td>44</td>
<td>44 to 130</td>
</tr>
<tr>
<td>ferric carboxymaltose *</td>
<td>600mg intravenous dose once weekly</td>
<td>-</td>
<td>130</td>
</tr>
<tr>
<td>iron sucrose *</td>
<td>200mg intravenous dose one to three times per week</td>
<td>17</td>
<td>17 to 51</td>
</tr>
<tr>
<td>iron dextran</td>
<td>200mg intravenous dose one to three times per week</td>
<td>16</td>
<td>16 to 48</td>
</tr>
</tbody>
</table>

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 4 October 2010. *Costs from Monthly Index of Medical Specialities September 2010.

Additional information: budget impact

Based on current prescribing of iv iron preparations, it was estimated that 2,439 non-dialysis renal patients in Scotland received treatment with iron sucrose at a dose of 1,000mg in 2009 and 146 received iron dextran. The manufacturer estimated that if patients receiving iv iron sucrose and dextran were to receive ferric carboxymaltose instead then the net medicines budget impact would be £343k per year. These estimates assumed that all patients would be switched to ferric carboxymaltose and may therefore be an overestimate.
References

The undernoted references were supplied with the submission.


This assessment is based on data submitted by the applicant company up to and including 12 November 2010.

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.