

iron isomaltoside 1000, 100mg/mL solution for injection/infusion (Monofer®) SMC No. (697/11)

Pharmacosmos UK

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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 full submission

iron isomaltoside 1000 (Monofer®) is accepted for restricted use within NHS Scotland.

Indication under review: Treatment of iron deficiency anaemia in the following conditions:

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

SMC restriction: 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.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Treatment of iron deficiency anaemia in the following conditions:

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

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

Dosing Information

The dose and dosage schedule for iron isomaltoside 1000 must be individually established for each patient based on a calculation of the total iron deficit. The optimal haemoglobin target level may vary in different patient groups.

Intravenous bolus injection:

Iron isomaltoside 1000 may be administered as a 100 to 200mg intravenous bolus injection up to three times a week at an administration rate of up to 50mg iron/minute. It may be diluted in 10 to 20mL sterile 0.9% sodium chloride.

Total dose infusion (TDI):

Iron isomaltoside 1000 may be administered as a total dose infusion in which the total iron dose is given in a single infusion. Iron isomaltoside 1000 given as total dose infusion is administered as a single dose of up to 20mg iron/kg body weight as an intravenous drip infusion.

The intravenous administration of iron isomaltoside 1000 by the total dose infusion method should be restricted to hospital use only.

Intravenous drip infusion:

Iron isomaltoside 1000 may be administered in doses of 200 to 1,000mg once every week until the total iron dose has been administered.

Product availability date

18 January 2010

Summary of evidence on comparative efficacy

Iron isomaltoside 1000 (hereafter referred to as iron isomaltoside) contains iron in a strongly bound complex that enables a controlled and slow release of bioavailable iron to iron-binding proteins with little risk of free iron. Isomaltoside 1000 consists of 3-5 glucose units primarily, and comes from a chemical modification of isomalto-oligosaccharides present in Dextran 1. Dextran 1 is used in the prevention of anaphylactic reactions to clinical dextran infusions for plasma volume expansion and therefore may reduce the risk of anaphylactic/anaphylactoid or delayed allergic reactions when combined with iron in the iron isomaltoside formulation.

The submitting company has requested that the Scottish Medicines Consortium (SMC) consider the use of this product in a sub-population of the licensed indication namely the population described by the licensed indication with the exception of patients receiving haemodialysis. The

manufacturer has stated that patients with chronic renal disease receiving haemodialysis should not be considered as part of the submission.

Two multi-centre open-label non-comparative studies have been conducted in patients aged at least 18 years with iron deficiency anaemia, serum ferritin <800 microgram/L, a life expectancy >12 months and chronic kidney disease (CKD) in one study and chronic heart failure (CHF) in the other study. In the CKD study patients not currently treated with parenteral iron with a haemoglobin (Hb) \leq 11g/dL, or on dialysis and willing to switch their parenteral iron maintenance therapy to iron isomaltoside and with a Hb \leq 13g/dL were recruited. In the CHF study, patients were required to have Hb <11.5g/dL (females) or <12g/dL (males) following a protocol amendment. In both studies, safety was the primary endpoint and secondary endpoints included changes in Hb, ferritin, and haematocrit at week 8. All patients were treated with open-label iron isomaltoside 100mg to 200mg (iron) as four repeated intravenous (iv) bolus injections or as an iv total dose infusion (TDI). If the TDI exceeded 20mg iron/kg it was split into two doses with a one week interval between them. The infusion time was 30 minutes for a TDI <10mg/kg and 60 minutes for a TDI of 10 to 20mg/kg.

The CKD study recruited 182 patients; 40 patients received a TDI (mean dose=975mg) and 142 received bolus doses (mean bolus dose=105mg). The number of patients on dialysis was 161 and there were 21 pre-dialysis patients. Haemoglobin levels were significantly higher at week 8 compared to baseline. In the sub-group who were not currently treated with iv iron at enrolment (n=38), the mean Hb at baseline was 9.92g/dL and at week 8 was 11.12g/dL and in the sub-group who switched from an alternative iv iron preparation (n=144), the mean Hb at baseline was 11.49g/dL and at week 8 was 11.75g/dL. In the bolus-treated patients the mean change from baseline for Hb was 0.20g/dL and for TDI-treated patients was 0.98g/dL (p=0.015, for difference between bolus and TDI). Serum ferritin levels were also significantly higher at week 8, and although the percentage of transferrin saturation was higher at week 8, the difference relative to baseline was not significant.

In the CHF study, all 20 patients recruited received an iv TDI of iron isomaltoside. There was no significant difference in Hb level at week 8; mean change 0.44g/dL compared to baseline. Serum ferritin levels significantly increased from baseline at all visits and haematocrit levels were significantly higher than baseline at week 8 only. Quality of life (QoL) was measured using the linear analogue scale assessment (LASA) QoL questionnaire at baseline and at weeks 4 and 8. It measured energy level, ability to perform daily activities and overall QoL (on a 0 [worst] to 100mm linear analogue scale). The energy level score was 45 at baseline and significantly increased at week 4 (score=67) and week 8 (61). At baseline the ability to perform daily activities score was 47 and the increase was significant at week 4 (66) but not at week 8 (57). The overall QoL score was 57 at baseline and increased significantly at week 4 (70) but not at week 8 (64).

Summary of evidence on comparative safety

In the CKD study, 62% of patients experienced adverse events (AE) that were generally mild to moderate in intensity. Nineteen AE were classed as probably or possibly related to study medication; two were serious (unstable angina and *Staphylococcus aureus* infection). There were two deaths in the study and both were considered unrelated to the study drug.

In the CHF study, 65% (13/20) of patients experienced a total of 25 AEs, 18 of which were classified as non-serious and seven as serious. None of these events was considered probably or possibly related to study treatment. The numbers of patients with abnormalities on electrocardiogram (ECG) which were classified as clinically significant by the investigator were: four at baseline, two at week 1, two at week 2, one at week 4 and four at week 8. All ECG abnormalities could be explained by the patients' past medical histories. There were no deaths.

In both studies, no acute anaphylactic/anaphylactoid or delayed allergic reactions were reported and there were no clinically significant changes in routine clinical laboratory tests or vital signs. The summary of product characteristics for iron isomaltoside notes that TDI has been associated with an increased incidence of adverse reactions, in particular delayed hypersensitivity-like reactions.

Summary of clinical effectiveness issues

The submitting company has requested that the Scottish Medicines Consortium (SMC) consider the use of iron isomaltoside in patients who are eligible to receive intravenous iron within the licensed indication, with the exception of patients receiving haemodialysis. Haemodialysis patients were not considered in the economic analysis as the perceived benefits of the product would not apply in this patient cohort as standard practice involves the use of low doses of iron during planned hospital visits for dialysis.

The two studies included in the company's submission were open-label and of non-comparative design and recruited relatively small numbers of patients. However data from these studies were sufficient to prove the efficacy and safety of iron isomaltoside to the Swedish licensing authority. Marketing authorisations have been granted throughout Europe including the UK based on "well established use". In the larger study 88% of patients were on dialysis however, patients on haemodialysis were excluded by the submitting company in their submission to SMC. Therefore, efficacy data are available for only a limited number of patients relevant to the population under consideration by SMC.

Comparative efficacy and safety of iron isomaltoside is unknown relative to other iv iron preparations. The regulatory authority considered that there were no significant unexpected safety findings compared to other parenteral iron preparations. However, they were unable to conclude that the safety profile iron isomaltoside was superior to that of other iron carbohydrate complexes. It was noted that the possibility of anaphylactoid reactions with iron isomaltoside cannot be excluded.

Potential advantages of iv iron isomaltoside include the ability to administer as a TDI (over one hour for doses of 10 to 20mg iron/kg body weight) and no requirement for a test dose. Iron dextran (Cosmofer®) may be given as a TDI over 4 to 6 hours and requires a test dose. Ferric carboxymaltose (Ferinject®) may be given as one infusion at doses up to 1,000mg (not exceeding 15mg iron/kg body weight) over 15 minutes and no test dose is required. These differences in administration of parenteral iron preparations may offer advantages to the service and the patient for iron isomaltoside. Experts consulted by SMC concurred with this view and considered the administration regimen of iron isomaltoside relative to comparators to be advantageous, particularly for patients requiring to travel significant distances to receive therapy. High dose infusion, short of full TDI, may also be used on occasion and the administration advantages for iron isomaltoside would also apply in this situation.

Summary of comparative health economic evidence

The manufacturer presented a cost-minimisation analysis comparing iron isomaltoside to a range of comparators: iron sucrose, iron dextran, ferric carboxymaltose and blood transfusions in non-dialysis-dependent patients. The economic analysis focused on the administration of iron as a total dose infusion and did not consider administration by IV bolus injection. The time period was the duration of a course of treatment for a TDI of iron. Based on SMC clinical experts' feedback the most appropriate comparators in the patient population under review are iron sucrose and iron dextran. The manufacturer made the assumption that all the iv iron products considered are clinically equivalent, although there was no formal consideration of the evidence base for iron isomaltoside or the comparators.

Resource use and costs associated with the differing administration needs for a TDI for iron isomaltoside and the comparators were considered. This covered the opportunity cost of nursing time, consumables costs and need for patient transportation. The manufacturer considered the costs for three illustrative iron dose requirements: 600mg, 1000mg and 1600mg. Scenarios were presented consisting of the involvement of a band 5 to 7 nurse and for each band, assumptions were applied concerning the percentage of patients requiring ambulance transportation to the clinic for their iron infusion.

Iron isomaltoside has a higher acquisition cost than the main comparators, but is associated with resource offsets due to more rapid drug administration. The analysis showed that iron isomaltoside administered in a single dose compared to iron sucrose administered over several visits was cost saving at all three dose levels. Savings were estimated at £85-£142 per treatment course for the 1000mg dose (which would require 5 clinic visits for iron sucrose), and £179-£233 for the 1600mg dose (with 8 clinic visits required for iron sucrose). Cost savings versus iron dextran, administered over a 6 hour period plus 10 minutes set up time, were estimated for the 600mg dose and ranged from an additional cost of £25 to a saving of £24 at the 1000mg dose. An additional cost was estimated for the 1600mg dose (£30-£79). Cost savings were estimated compared to ferric carboxymaltose and blood transfusions at all three dose levels.

In addition to the weak clinical evidence available for a non-haemodialysis patient population, there were a number of limitations in the analysis:

- Nursing time is a key driver for the resource offset advantages associated with iron isomaltoside. The results presented above used a relatively high cost to value nursing time which was not in line with the requirements for analyses submitted to SMC. However, the manufacturer subsequently submitted revised figures to use more appropriate nursing costs across differing grades of nurse input. The results indicated that iron isomaltoside was at all doses less costly than iron sucrose, assuming 50% of patients required transport. In comparison with iron dextran, iron isomaltoside was more expensive at all doses other than when a 600mg dose was assumed alongside band 7 nursing time.
- The lack of a clear base case meant that it was difficult to establish the relevant average dosage used in clinical practice in Scotland, and therefore the most plausible estimates for incremental costs or savings with iron isomaltoside versus iron dextran or sucrose. The mean TDI dose in the iron isomaltoside studies was less than 1000mg.

- Infusion time for iron dextran was estimated at 6 hours without any practice-based clinical justification provided, whereas the summary of product characteristics states a range of 4-6 hours. Additional analysis provided by the manufacturer applying a shorter infusion time of 5 hours reduced cost savings at the lower dose and increased the incremental cost of iron isomaltoside at the higher doses.
- The health economic case focused on the TDI schedule and therefore the cost-effectiveness of iron isomaltoside given as an iv bolus is not known.

Despite these limitations, the economic case was considered demonstrated for administration of iron isomaltoside by high dose infusion within the licensed indication, excluding use in patients with chronic kidney disease receiving haemodialysis.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

A number of guidelines covering a range of therapeutic areas including obstetrics, renal medicine, inflammatory bowel disease and cancer advocate the use of intravenous iron in specific clinical circumstances. These guidelines predate the availability of iron isomaltoside.

Additional information: comparators

The following intravenous iron preparations may be considered as comparators; ferric carboxymaltose, iron dextran and iron sucrose, as well as blood transfusions.

Cost of relevant comparators

Drug	Intravenous bolus injection	Cost per week (£)
Iron isomaltoside 1000	200mg iv three times weekly	102
Ferric carboxymaltose	200mg iv three times weekly	115
Iron sucrose	200mg iv three times weekly	56
Iron dextran	200mg iv three times weekly	49
Drug	Total dose infusion regimen	Cost per treatment (£)
Iron isomaltoside 1000	15 to 20mg iron/kg body weight iv infusion	170 to 237
Ferric carboxymaltose	15mg iron/kg body weight iv infusion*	191
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. Costs from eVadis on 19 January 2011 and on 07 March 2011. iv=intravenous. Total dose infusion regimen based on a body weight of 70kg (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 estimate of budget impact provided by the manufacturer consisted of an additional drug cost per year of around £22k if iron sucrose is displaced in non-dialysis-dependent CKD patients (estimated to be 164 patients in Scotland), or an additional drug cost of about £24k if iron dextran is instead displaced in the same number of patients. Overall, the manufacturer estimated net cost savings due to the resource savings associated with iron isomaltoside.

References

The undernoted reference was supplied with the submission.

Public Assessment Report; Scientific Discussion. Monofer 100mg/ml solution for injection/infusion iron (III) isomaltoside 1000. Swedish Regulatory Authority. Ref. SE/H/734/01/DC. 26th November 2009.

This assessment is based on data submitted by the applicant company up to and including 11 March 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.