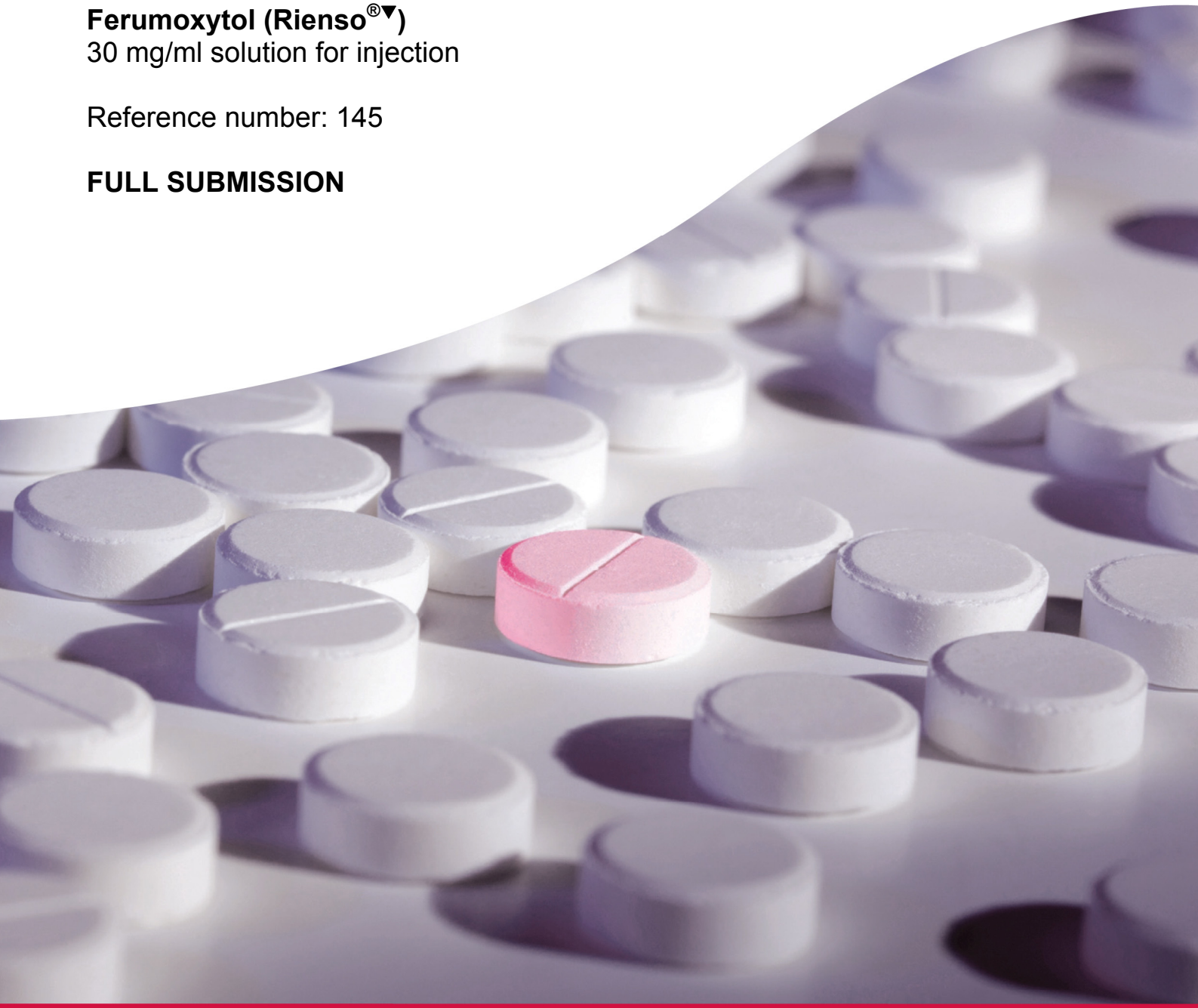
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Ferumoxytol (Rienso®▼)
30 mg/ml solution for injection

Reference number: 145

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Ferumoxytol (Rienso®▼) 30 mg/ml solution for injection

This assessment report is based on evidence submitted by Takeda UK Ltd on 28 November 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Ferumoxytol (Rienso®▼) is indicated for the intravenous treatment of iron deficiency anaemia in adult patients with chronic kidney disease. The diagnosis of iron deficiency must be based on appropriate laboratory tests[2].
Dosing	The recommended course of ferumoxytol is either one or two doses of 510 mg, based on the patient's pre-treatment haemoglobin concentration and body weight. For patients receiving two doses, the second 510 mg intravenous injection is to be administered 2 to 8 days later. Refer to the Summary of Product Characteristics (SPCs) for further information regarding the recommended dosing schedule. Each 510 mg ferumoxytol dose is administered as an undiluted intravenous injection delivered at a rate of up to 1 ml/sec (30 mg/sec); a minimum of 17 seconds is therefore required to administer one 510 mg dose. Following each ferumoxytol injection, patients should be monitored for signs and symptoms of hypotension and/or hypersensitivity for at least 30 minutes[2].
Marketing authorisation date	15 June 2012[2].

2.0 DECISION CONTEXT

2.1 Background

Anaemia is the clinical manifestation of a decrease in the quality and/or quantity of circulating red blood cells, and is defined as a blood haemoglobin (Hb) concentration lower than a cut-off of 12 g/dl in non-pregnant women and 13 g/dl in men[3]. Anaemia develops early in the course of chronic kidney disease (CKD), and more severe grades of CKD are associated with a higher prevalence and severity of anaemia[3,4]. The population prevalence of stage 3–5 CKD (estimated glomerular filtration rate [eGFR] less than 60 ml/min/1.73 m^2; see Glossary for disease stage definitions) has been estimated by one UK study to be 4.9%, and of these patients around 12% met the criteria for anaemia[3,5].

Iron deficiency is a frequent cause of anaemia in CKD patients and can have multiple causes, including iron sequestration due to inflammatory processes and reduced dietary iron intake or absorption[6]. National Institute for Health and Clinical Excellence (NICE) guidelines recommend that iron deficiency anaemia (IDA) in CKD patients should be diagnosed based on serum ferritin levels, while functional iron deficiency (where utilisation of iron in red cell production is impaired) should be diagnosed based on levels of hypochromic red cells or transferrin saturation (TSAT; see Glossary)[7].

Iron management forms an essential part of the treatment of anaemia associated with CKD; although therapy typically involves treatment with oral iron, where this cannot be used or is ineffective, intravenous (IV) formulations should be administered[3,7]. Ferumoxytol (Rienso®▼) is an IV preparation containing iron sequestered in an iron-carbohydrate complex, which isolates the iron oxide core until the complex enters the liver, spleen and bone marrow, where the iron is released intracellularly from its carbohydrate shell[2,6].

Ferumoxytol is indicated for IV treatment of IDA in adult CKD patients[2]. However, the applicant company has requested that AWMSG consider the use of ferumoxytol for the treatment of IDA in non-haemodialysis dependent adult CKD patients when oral iron is ineffective or cannot be used[1].

2.2 Comparators

The comparators requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) were the following IV iron preparations:

- Ferric carboxymaltose (Ferinject®)
- Iron dextran (CosmoFer®)
- Iron isomaltoside 1000 (Monofer®▼)
- Iron sucrose (Venofer®)

The company submission does not consider iron isomaltoside 1000 as a relevant comparator; the company state that this is due to a lack of use of this medicine in Welsh clinical practice (refer to Section 4.1.1 for further discussion)[1].

Although the licensed indication for ferumoxytol does not preclude its use as a direct alternative to oral iron preparations, national guidelines[7] and expert opinion received by AWTTC both recommend the use of IV iron preparations when oral iron cannot be used or is ineffective.

2.3 Guidance and related advice

- Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO clinical practice guideline for anemia in chronic kidney disease (2012)[8].
- NICE. Clinical Guideline 114. Anaemia management in people with chronic kidney disease (2011)[7].
- National Kidney Foundation. KDOQI [Kidney Disease Outcomes Quality Initiative] clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease (2006)[4].
- European Best Practice Guidelines. Revised European best practice guidelines for the management of anaemia in patients with chronic renal failure (2004)[9].

The All Wales Medicines Strategy Group (AWMSG) has previously issued recommendations for the use of ferric carboxymaltose:

- Ferric carboxymaltose (Ferinject®) is recommended as an option for use within NHS Wales for the treatment of patients with iron deficiency when oral iron preparations are ineffective or cannot be used. Ferric carboxymaltose (Ferinject®) should be restricted for use in non-haemodialysis patients only (2011)[10].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

3.1 Comparative effectiveness

As evidence of comparative effectiveness, the company submission presents one phase II study evaluating ferumoxytol and iron sucrose; three phase III studies comparing ferumoxytol against oral iron; and a mixed treatment comparison (MTC) designed to compare the clinical effectiveness of ferumoxytol to a range of other IDA treatments in CKD patients[1]. No oral iron preparations were requested as comparators by AWTTC, for the reasons outlined in Section 2.2, and therefore evidence comparing ferumoxytol with oral iron is of limited relevance to the scope of this appraisal. However, as these studies have been incorporated into the MTC, methods and results are presented briefly in Section 3.1.2 and Appendix 1.

The submission also includes one study that examined the impact any variations in real-world clinical administration practice may have on the effectiveness of ferumoxytol[11]. Over the one-year study period, haemodialysis patients maintained Hb within target range (10 to 12 g/dl), regardless of whether they received ferumoxytol as a full course (1,020 mg) or as a single injection (510 mg)[11]. Since this study does not provide evidence of the comparative effectiveness of ferumoxytol versus other IV iron formulations, it will not be discussed further.

3.1.1 The ferumoxytol compared to iron sucrose trial (FIRST) study

This multicentre, randomised, open-label, phase II trial compared ferumoxytol and iron sucrose in patients (≥ 18 years) with CKD stages 1–5 and 5D (see Glossary)[12,13]. Patients (n = 162) were randomised (1:1) to receive either ferumoxytol (n = 80; total cumulative dose of 1,020 mg as an IV injection) or iron sucrose (n = 82; total cumulative dose of 1,000 mg as a slow IV injection or IV infusion). Ferumoxytol was administered as two 510 mg IV injections within 5 ± 3 days in both haemodialysis and nondialysis patients. Iron sucrose was administered as 100 mg doses at ten consecutive dialysis sessions within three weeks in haemodialysis patients and 200 mg doses at five nonconsecutive visits within approximately 14 days in nondialysis patients[12,13].

The study enrolled patients with eGFR < 60 ml/min/1.73 m^2 (or diagnosis of CKD), Hb levels < 11 g/dl (but ≥ 7 g/dl) and TSAT < 30%. Main exclusion criteria were a history of allergy to IV iron, recent or planned blood transfusions, peritoneal dialysis, cause of anaemia other than iron deficiency, and recent or anticipated initiation, disruption or dose change (> 20%) in erythropoiesis-stimulating agent (ESA) therapy[12,13].

The primary objective of this study was to evaluate the safety of IV ferumoxytol compared to IV iron sucrose at the stated doses (see safety data in Section 3.2); an additional objective evaluated the efficacy of ferumoxytol as compared to iron sucrose by assessing changes in Hb from baseline to week 5. The mean change in Hb levels from baseline to week 5 was 0.71 g/dl for ferumoxytol-treated patients compared with 0.61 g/dl for the iron sucrose group (0.84 g/dl versus 0.74 g/dl when adjusted for baseline Hb and dialysis status; difference 0.1 g/dl; [commercial in confidence data removed]; p = 0.515)[12,13]; [commercial in confidence data removed]. Mean Hb levels increased more rapidly in ferumoxytol-treated patients than those in the iron sucrose group, and this was most marked at week 2, when mean change from baseline was 0.52 g/dl versus 0.19 g/dl[12,13]. More patients in the ferumoxytol group had an Hb level increase ≥ 1.0 g/dl between baseline and week 5 than in the iron sucrose group (40 [50%] versus 34 [41.5%])[12,13].

[Commercial in confidence data removed]

3.1.2 Ferumoxytol versus oral iron supplements

The company submission included three randomised, multicentre, controlled, open-label phase III trials that evaluated the safety and efficacy of ferumoxytol for the treatment of IDA in haemodialysis-dependent (study 62,745-5) and nondialysis-dependent (study 62,745-6 and study 62,745-7) CKD patients[1,14–16]. Further details regarding study design and endpoints are presented in Appendix 1.

In all three studies, the mean increase in Hb levels at day 35 was significantly higher in the ferumoxytol group when compared with oral iron (study 62,745-5: 1.02 g/dl versus 0.46 g/dl, $p = 0.0002$; study 62,745-6: 0.82 g/dl versus 0.16 g/dl, $p < 0.0001$; study 62745-7: 1.22 g/dl versus 0.52 g/dl, $p < 0.0001$)[14–16]. Similar beneficial effects were observed during analysis of secondary endpoints.

3.1.3 Mixed treatment comparison

As there were no data directly comparing ferumoxytol with ferric carboxymaltose, iron dextran or iron isomaltoside 1000, a systematic review and MTC have been included in the company submission to evaluate the relative efficacy of these treatments with regard to improvement of Hb levels in CKD patients with IDA[1].

The systematic review, conducted in November 2010, included all randomised controlled trials that compared iron preparations in CKD patients with IDA, regardless of trial design (parallel, crossover, open label, single or double blind), date of publication or language[17]. Studies must have reported either change in Hb level from baseline, or absolute Hb level at the beginning and end of the study. Methods and results of the 18 studies identified by the systematic review and chosen for inclusion in the MTC are summarised in Appendix 1, Table 1A.

The MTC utilised the methods of Lu and Ades (2004) for combining direct and indirect studies[18,19]. The results comparing outcomes for ferumoxytol with the most relevant comparators are presented in Table 1. No significant differences in efficacy were identified between ferumoxytol and other IV iron formulations[1,19]. In order to diminish study heterogeneity, the MTC network was further reduced by excluding studies where duration exceeded 60 days, resulting in the inclusion of only nine studies; there remained no significant difference between ferumoxytol and other IV iron formulations. A second efficacy analysis was performed, measuring serum ferritin change data from 16 studies where this was reported. This analysis also found no significant difference in outcomes between ferumoxytol and other IV iron preparations[1,19].

Table 1. Differences in outcomes between ferumoxytol and comparators estimated from the MTC[1,19].

Comparison	Difference in change from baseline in mean Hb g/dl (95% CrI)	Difference in change from baseline in mean serum ferritin microgram/dl (95% CrI)
All eligible studies	*N = 18 studies*	*N = 16 studies*
Ferric carboxymaltose vs. ferumoxytol	−0.004 (−3.34, 3.23)	−97.5 (−311, 125)
Iron sucrose vs. ferumoxytol	−0.381 (−2.45, 1.64)	85.6 (−47.4, 224)
Iron dextran vs. ferumoxytol	−0.029 (−2.22, 2.29)	−19.0 (−213, 164)
Studies of ≤ 60 days duration	*N = 9 studies*	*NR*
Ferric carboxymaltose vs. ferumoxytol	−0.005 (−0.94, 0.96)	NR
Iron sucrose vs. ferumoxytol	−0.376 (−1.11, 0.26)	NR
Iron dextran vs. ferumoxytol	−0.405 (−1.40, 0.55)	NR
CrI: credible intervals; Hb: haemoglobin; NR: not reported.		

3.2 Evidence of comparative safety

Comparative safety evidence for ferumoxytol versus iron sucrose is available from the FIRST study. Attempts were also made to analyse adverse event (AE) profiles for ferumoxytol with all IV iron treatments as part of the MTC. However, the authors concluded that the results of this analysis were not robust enough to report, due to a lack of synthesisable evidence for AEs within the chosen studies[19].

The overall incidence of patients reporting AEs during the FIRST study was lower in ferumoxytol-treated patients than in those receiving iron sucrose (38/80 [47.5%] versus 53/82 [64.6%]). These AEs were considered treatment-related in 10.0% and 15.9% of patients in the ferumoxytol and iron sucrose groups respectively[12,13]. Serious AEs (SAEs) were experienced by seven patients in the ferumoxytol group and six patients receiving iron sucrose, and were considered treatment-related in one patient from each group (one ferumoxytol-treated patient experienced an anaphylactic reaction while one patient in the iron sucrose group experienced hypotension). Discontinuation due to AEs occurred in five patients (one had received ferumoxytol versus four iron sucrose-treated patients)[12,13]. No deaths occurred during the study[12]. The most frequently reported AEs in ferumoxytol-treated patients included nausea (7.5% of ferumoxytol-treated patients versus 3.7% of the iron sucrose group), muscle spasms (5.0% versus 7.3%, respectively), nasopharyngitis (3.8% versus 2.4%), headache (3.8% versus 2.4%), cough (3.8% versus 0), hyperkalaemia (3.8% versus 1.2%) and urinary tract infection (3.8% versus 7.3%)[12].

The submission also includes safety data from the one-year study into real-world effectiveness of ferumoxytol (see Section 3.1), where 8,666 patients received a total of 33,358 ferumoxytol doses. A total of 108 patients (1.25%) experienced AEs; these were considered to be SAEs in 18 patients (0.21%) and led to treatment discontinuation in 49 patients (0.57%)[1].

At the time of licensing, the Committee for Medicinal Products for Human Use (CHMP) reviewed the safety data available for ferumoxytol versus oral iron, which included studies 62,745-5, 62,745-6 and 62,745-7[6]. AEs were experienced in approximately 35%–55% of ferumoxytol-treated patients, and were numerically similar or lower in comparison than those receiving oral iron. Further, no AE was reported in more than 10% of patients in these studies. CHMP also concluded that the ferumoxytol safety

profile appears similar to other EU-authorised IV iron preparations. However, the assessment report compiled by CHMP also includes a divergent position expressed by five CHMP members, which considered the benefit-risk ratio to be negative[6], based on an analysis of AEs in patients receiving IV iron preparations reported to the Food and Drug Administration (FDA) from October 2009 to June 2010[20]. This study identified higher AE rates in patients receiving ferumoxytol or iron dextran than in those treated with iron sucrose or sodium ferric gluconate. Increased reporting of AEs in ferumoxytol-treated patients was expected by the study author, due to the "Weber effect": the tendency toward higher AE reporting rates for a newly available treatment relative to other agents in the same class[20]. Additionally, an FDA-conducted study of AE reports associated with IV iron treatments (from initial marketing date to mid-April 2007) concluded that it was difficult to calculate incidence rates and relative risk estimates based on voluntarily submitted AE data due to underreporting, possible differential product reporting and lack of data regarding the number of doses received, among other reasons[21]. A response to the study by Bailie, co-authored by a Medical Officer from the FDA, stated that calculating proportional reporting ratios and odds ratios of AEs from this data is not appropriate, since the reporting system is voluntary, passive, and spontaneous[22].

3.3 AWTTC critique

- The applicant company has requested that AWMSG consider the use of ferumoxytol for the treatment of IDA in non-haemodialysis dependent adult CKD patients when oral iron is ineffective or cannot be used[1].
- The company submission includes a direct comparison of ferumoxytol with iron sucrose and oral iron, in addition to an MTC comparing ferumoxytol with other IV iron preparations[1]. The studies utilised differed with regard to inclusion and exclusion criteria, disease severity, baseline population characteristics, dialysis status at study enrolment, endpoint definitions, use of ESA therapies and dosing regimens received. Further, although most studies reported an intent-to-treat analysis, some did not report data for this population[1]. Additionally, during one study (Stoves et al, 2001), the erythropoietin dose was adjusted according to a pre-arranged protocol in order to achieve similar Hb outcomes in the two groups[23]. Due to these differences in methodology and patient population, the findings of the MTC should be interpreted with caution.
- The literature search informing the MTC was conducted in November 2010[1], and it is unclear if an updated literature search has been undertaken to identify additional resources that could inform the MTC. For example, AWTTC literature searches have identified a Cochrane review, published in 2012, of parenteral versus oral iron therapy for patients with CKD[24]. Furthermore, the FIRST study has not been included in the MTC; the applicant company has confirmed that this was not included as the results had not been published in a peer-reviewed publication (refer to Section 4.1.3 for further discussion).
- It is unclear to what extent the outcomes of the MTC reflect outcomes in the subpopulation highlighted by the company (non-haemodialysis dependent adult CKD patients when oral iron is ineffective or cannot be used), as the MTC included studies where patients were undergoing dialysis[1]. A report on the MTC requested by AWTTC and supplied by the company (but not included within the original company submission) includes an analysis of non-haemodialysis CKD patients; this demonstrated no statistically significant differences in change from baseline in Hb for ferumoxytol and the comparators (see Section 4.1.3 for further details).
- The data most relevant to a comparison of ferumoxytol versus IV iron preparations comes from the FIRST study. The related evidence presented in the company submission is drawn from a clinical study report and a poster presentation; at the time of writing, results of this study have not been published in any peer-reviewed publication[12,13]. Criteria for inclusion of patients into this study did not take into account serum ferritin or hypochromic red cells, as

recommended by NICE for diagnosis of IDA (see Glossary), and therefore the studied patient population may not reflect eligible IDA patients seen in clinical practice in the UK[7,12,13]. A subgroup analysis in nondialysis patients was included, but did not meet the prespecified noninferiority criteria; this was met in the equivalent haemodialysis subgroup[12]. However, the ability to draw clinically meaningful conclusions is limited by the small number of subjects in the subgroups.

- Unlike iron sucrose and iron dextran, ferumoxytol requires no test dose before initiation of therapy[2,25,26]. Additionally, ferumoxytol IV injection requires a shorter administration in comparison to iron sucrose, iron dextran, ferric carboxymaltose and iron isomaltoside 1000, and can be administered less frequently than iron sucrose, ferric carboxymaltose and iron isomaltoside 1000[2,25–28], which may impact on patient preference.
- There is limited data available regarding the safety and efficacy of ferumoxytol for repeated or long-term administration. This is reflected in the Risk Management Plan[6].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost minimisation analysis (CMA) of ferumoxytol (Rienso®▼) in its licensed indication for the treatment of iron deficiency in adult patients with CKD[1]. The population covered in this submission is a subset of the licensed indication population comprising non-haemodialysis dependent adult patients with CKD for whom oral iron preparations are ineffective or cannot be used.

In the economic analysis, ferumoxytol is compared with alternative IV iron replacement therapies for the delivery of a 1,000 mg dose of iron to treat an acute episode of IDA in non-haemodialysis dependent CKD patients. The primary comparator is iron sucrose; other comparators considered are ferric carboxymaltose and iron dextran. Based on market analysis data and interviews with specialist nurses in Wales, iron isomaltoside1000 is not considered as a comparator due to reported low levels of use in practice. The economic analysis assumes equal efficacy among all IV iron replacement therapies. This is based on the results of a network meta-analysis that provides adjusted indirect treatment comparisons of studies that utilised oral iron therapies as the reference comparator. Change from baseline in Hb levels is used as the primary outcome measure. The IV iron replacement therapies considered have been assumed to have a similar overall safety profiles.

Three methods of administration are considered in the analysis: IV bolus injection, IV drip infusion and TDI (total dose infusion), depending on the comparator. The total repletion dose required for treatment of an acute episode of IDA in non-haemodialysis dependent CKD patients, and used in the base case analysis, is 1,000 mg iron. The need for initial test dose is taken into account where recommended.

Data on time estimates and resource utilisation covering the delivery and related tasks associated with administration of each of the comparator IV irons are collected using a European survey of renal nurses commissioned by the applicant company, with representation from one centre in Wales. The estimates driven from the survey were validated in interviews with four specialist nurses from Wales.

Comparator drug costs are based on British National Formulary (BNF) 64[29] and Monthly Index of Medical Specialities (MIMS)[30] prices while ferumoxytol price is based on company information. Unit costs of IV administration instruments are derived either

from a published study on the costs associated with IV iron replacement therapies[31] or from a medical equipment wholesaler price list[32] and inflated to 2011 prices. Unit costs applied to nurse time are based on Personal Social Services Research Unit (PSSRU) unit costs[33]. Funded transport unit costs are based on Information Services Division (ISD) Scotland data[34].

The time horizon is five weeks to cover the maximum expected duration of a course of IV iron replacement therapy to treat an acute episode of iron deficiency anaemia.

4.1.2 Results

The results of the base case analysis are presented in Table 2. The results show that ferumoxytol delivered by bolus injection cost less to deliver a 1,000 mg repletion course of iron than the primary comparators of ferric carboxymaltose, iron sucrose and iron dextran.

Table 2. Base case analysis results.

Base case comparison	Total costs per IDA treatment course			Plausibility
	Ferumoxytol	Comparator	Difference	
Ferumoxytol (bolus injection) vs. ferric carboxymaltose				
Ferric carboxymaltose bolus injection	£184	£251	−£67	Assumption of equivalence of efficacy based on indirect comparisons. Administration times are based on the expert opinion of four specialist nurses
Ferric carboxymaltose drip infusion	£184	£268	−£84	
Ferumoxytol (bolus injection) vs. iron sucrose				
Iron sucrose bolus injection	£184	£236	−£52	Assumption of equivalence of efficacy based indirect comparisons. Administration times are based on the expert opinion of four specialist nurses
Iron sucrose drip infusion	£184	£300	−£116	
Ferumoxytol (bolus injection) vs. iron dextran				
Iron dextran bolus injection	£184	£229	−£45	Assumption of equivalence of efficacy based on indirect comparisons. Administration times are based on the expert opinion of four specialist nurses
Iron dextran drip infusion	£184	£292	−£108	
Iron dextran TDI	£184	£194	−£10	

The company reported results for a range of sensitivity and scenario analyses. In most of these analyses, ferumoxytol remains cost saving. The scenario and sensitivity analyses where ferumoxytol ceased to be cost saving are where ferumoxytol is compared with iron dextran. Results of the key scenario and sensitivity analyses are presented in Tables 3 and 4, respectively.

Table 3. Scenario analyses results.

Base case comparison	Total costs per IDA treatment course			Plausibility
	Ferumoxytol	Comparator	Difference	
Scenario 1: Using SPC administration times.	£197	Iron dextran bolus injection £273	-£76	SPC administration time seems to be a more plausible assumption.
		Iron dextran TDI £197	£0	
Scenario 2: Ferric carboxymaltose administration in a single visit.	£184	Ferric carboxymaltose bolus injection £223	-£39	Cost saving is demonstrated for both comparators. Administration frequency will be dependent on local practice and patient characteristics.
		Ferric carboxymaltose drip infusion £229	-£45	
Scenario 3: 800 mg iron delivered by comparator.	£184	Iron dextran bolus injection £189	−£5	Although 1,000 mg has been reported as the most commonly used iron dose, lower doses can also be used in practice depending on patient weight. A weighted average of the different doses reported would be a more plausible estimate.
		Iron dextran drip infusion £241	−£57	
		Iron dextran TDI £179	+£5	

Table 4. Sensitivity analyses results.

Base case comparison		Total costs per IDA treatment course			Plausibility
		Ferumoxytol	Comparator	Difference	
Patient to nurse ratio for delivery of iron dextran drip infusion/TDI (ferumoxytol vs iron dextran TDI) (base case ratio: 3 patients:1 nurse)					
2 patients:1 nurse		£184	£215	−£31	Nurses are likely to be observing more than one patient at a time. Each scenario plausible.
4 patients:1 nurse		£184	£184	£0	
NHS-funded transport use (base case: 30% of non-haemodialysis CKD patients)					
10%	Ferric carboxymaltose bolus injection	£164	£231	−£67	The values used in the sensitivity analysis (10% and 50%) are based on values reported by four specialist renal nurses while the base case value represents the midpoint of this reported range. The cost of patient transport is based on Scottish data.
	Ferric carboxymaltose drip infusion		£248	−£84	
	Iron dextran TDI		£184	−£20	
50%	Ferric carboxymaltose bolus injection	£203	£270	−£67	
	Ferric carboxymaltose drip infusion		£287	−£84	
	Iron dextran TDI		£202	+£1	

4.1.3 AWTTC critique

The reliability of the company's CMA is dependent on the extent to which ferumoxytol is considered to be therapeutically equivalent to the comparator IV iron replacement therapies. To support the assumption of equivalent efficacy, the company reported the results of a network meta-analysis that provides adjusted indirect treatment comparisons; however, as direct evidence from the FIRST trial of ferumoxytol versus iron sucrose[13] is not included, it is unclear if the network of evidence is complete, and the absence of all relevant evidence might introduce bias in the analysis. The trials included in the main MTC do not reflect the restricted patient population proposed by the company for use of ferumoxytol (non-haemodialysis patients in whom oral therapy is ineffective or cannot be used), being conducted as they were in haemodialysis and non-haemodialysis patients who could receive oral iron treatments (see Appendix 1). The company reported that the cost savings expected, compared to iron sucrose and iron dextran, are largely dependent on savings in nursing time, transport and equipment costs, which are based on expert opinion.

Strengths of the economic evidence:

- The company conducted a systematic review to identify trials of comparators for inclusion in a network meta-analysis.
- A range of sensitivity and scenario analyses has been conducted to explore the impact of changing key assumptions and parameter values.

Limitations of the economic evidence:

- The company submission only considers the use of ferumoxytol in non-haemodialysis patients where oral therapies are ineffective or cannot be used. As the trials of ferumoxytol and the comparators included in the network meta-analysis all randomised patients to either ferumoxytol or oral iron therapy, the trial populations are not reflective of the intended patients in practice. These trials also enrolled both dialysis and non-dialysis CKD patients. The company has provided a separate report (refer to Section 3.3) detailing the results of indirect comparisons from trials in non-haemodialysis CKD patients only, which also demonstrates no statistically significant differences in change from baseline in Hb for ferumoxytol and the comparators; however, this and all other analyses have resulted in wide credible intervals (CrI) around treatment differences, reflecting the network uncertainty.
- The evidence included in the network meta-analysis appears to be incomplete, as the FIRST trial that compared ferumoxytol directly with iron sucrose has been excluded[13]. [Commercial in confidence data removed]. The exclusion of this trial from the network of evidence would bias the results of the analysis in favour of ferumoxytol. The network also included trials using widely different doses of iron sucrose which may not reflect use in practice in the intended patient population (see Appendix 1).
- AEs were not formally analysed in the network meta-analyses; equivalence of the IV iron treatments' safety profiles is therefore based on assessment of efficacy only.
- In the absence of Welsh data, expert opinion has been used to inform resource use estimates, and unit costs of transportation are based on Scottish costs.
- Combined uncertainty in more than one parameter estimates has not been explored.
- The CMA approach precludes exploration of all but cost-related parameters; differences in patient convenience or preference arising from the different administration regimens is not considered.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published evidence on the cost-effectiveness of ferumoxytol within its current licensed indication.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company estimates the prevalence of IDA in non-haemodialysis patients in Wales to be 6,735 patients. This is based on data from the NICE CG114 costing report[35], Welsh population statistics[36], the UK Renal Registry report[37] and a Canadian study reporting 55% of non-dialysis patients to have a Hb level below 11g/dl[38]. Incidence is based on data from the UK Renal Registry report from 2011[37] and Welsh population statistics[36] and is reported to be 386 patients in 2012. An estimated mortality of 5.6% per annum for non-haemodialysis CKD patients from an observational study[39] is used in the analysis. The number of patients eligible for receiving iron replacement therapy is assumed to be 10% of the total number of non-haemodialysis patients with IDA. Hence, 672 patients are estimated to be currently on iron replacement therapies in Wales.

With an estimated market share of 10% in year 1 rising to 40% in year 5, the company anticipates the number of patients to receive ferumoxytol to be 67 patients in year 1, rising to 383 patients in year 5. The company anticipates this uptake will arise mainly from displacement of iron sucrose (60%), with smaller proportions from ferric carboxymaltose (30%) and iron dextran (10%), based on estimated current market shares.

5.1.2 Results

The company anticipates a net cost saving from switching to ferumoxytol. This is estimated to be £8,020 in year 1 rising to £42,130 in year 5. This saving is primarily driven by saving in nursing time, administration equipment and transport costs where iron sucrose or iron dextran are displaced, and by difference in drug costs where ferric carboxymaltose is displaced. The results are summarised in Table 5.

Table 5. Company-reported costs with the use of Rienso®▼ in non-haemodialysis patients with IDA

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients (indication(s) covered in this submission)	672	709	745	782	818
Uptake (%)	10%	20%	30%	35%	40%
Treated patients	67	145	232	290	353
Net costs					
Medication costs	+£332	+£713	+£1,147	+£1,431	+£1,774
Administration and monitoring	−£8,352	−£17,962	−£28,883	−£36,025	−£43,904
Primary care	N/A				
Secondary & tertiary care					
Staffing*	−£4,025	−£8,657	−£13,920	−£17,362	−£21,160
Infrastructure	N/A				
Personal social services					
Overall net cost	**−£8,020**	**−£17,249**	**−£27,736**	**−£34,594**	**−£42,130**
* Included also within administration and monitoring costs (nurse costs only).					

5.1.3 AWTTC critique of the budget impact analysis

- The company has considered the prevalence, incidence and mortality in their budget impact calculations; however, these values were based on assumptions and extrapolations from UK data and published evidence from Canada, which

may not be directly applicable to Wales. Hence, there is uncertainty around the patient numbers reported.

- The cost estimates are derived from the company CMA; therefore the limitations and uncertainties associated with the costs assumed in the CMA also apply to the budget impact analysis. Additionally, uncertainties exist around the reported market share and which products are expected to be displaced.
- Collectively, the budget impact calculations are subject to uncertainty that has not been explored in sensitivity analyses.

5.2 Table of comparative unit costs

AWTTC identified ferric carboxymaltose, iron sucrose solution for injection/infusion, iron dextran solution for injection/infusion and iron isomaltoside 1000 solution for injection/infusion as the most appropriate comparators for ferumoxytol in the treatment of IDA. Examples of acquisition costs for IV iron preparations are shown in Table 6, assuming delivery of 600 mg to 1,000 mg of elemental iron per episode of anaemia.

Table 6. Examples of acquisition costs for parenteral iron preparations.

Regimen	Example dose per patient per week*	Example acquisition cost†
Ferumoxytol (Rienso®▼) IV injection 30 mg/ml	Hb ≤ 10 g/dl: 2 x 510 mg Hb > 10–12 g/dl: Body weight ≤ 50 kg: 510 mg; Body weight > 50 kg: 2 x 510 mg Second injection to be given 2–8 days after the first injection.	£65 to £130
Ferric carboxymaltose (Ferinject®) IV solution 50 mg/ml	600–1,000 mg once weekly	£114.60 to £191.00
Iron sucrose (Venofer®) IV solution 20 mg/ml	200 mg maximum of three times weekly – 200 mg five times over two weeks	£61.44 to £102.40
Iron dextran (CosmoFer®) IV solution 50 mg/ml	600–1,000 mg once weekly	£47.82 to £79.70
Iron isomaltoside 1000 (Monofer®▼) IV solution 100 mg/ml	600–1,000 mg once weekly	£101.70 to £169.50

*The adequate dose is calculated for each patient individually.
†Costs are based on current BNF[29] or MIMS[30] list prices as of 8 January 2013, for delivering up to 1,000 mg elemental iron.
This table does not imply therapeutic equivalence of drugs or the stated doses.
See relevant SPCs for full dosing details[2,25,26,28,40].

6.0 ADDITIONAL INFORMATION

6.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, ferumoxytol (Rienso®▼) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search
Date of evidence search: 17 December 2012
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Stages of chronic kidney disease (CKD)[8]

CKD stage	Description	GFR (ml/min per 1.73 m^2)
1	Kidney damage with normal or increased GFR	≥ 90
2	Kidney damage with mild decreased GFR	60–89
3	Moderate decreased GFR	30–59
4	Severe decreased	15–29
5*	Kidney failure	< 15 (or dialysis)

CKD: chronic kidney disease; GFR: glomerular filtration rate.
CKD 1–5T notation applies to kidney transplant recipients.
* 5D if dialysis (haemodialysis or peritoneal dialysis).

Iron deficiency anaemia (IDA)

NICE guidelines recommend that IDA should be diagnosed in patients with stage 5 CKD with a ferritin level of less than 100 micrograms/l and considered in people with stage 3 and 4 CKD if the ferritin level is less than 100 micrograms/l[7]. In CKD patients with serum ferritin levels greater than 100 micrograms/l, functional iron deficiency (where storage iron levels may be adequate, but utilisation in red cell production is impaired) should be identified where the percentage of hypochromic red cells is greater than 6% or where transferrin saturation (TSAT) is less than 20%[3,7].

REFERENCES

1 Takeda UK Ltd. Form B: Detailed appraisal submission. Ferumoxytol (Rienso®▼). Nov 2012.

2 Takeda UK Ltd. Rienso®▼. Summary of Product Characteristics. Jul 2012. Available at: http://www.medicines.org.uk/EMC/medicine/26773/SPC/Rienso/. Accessed Jan 2013.

3 National Institute for Health and Clinical Excellence, National Clinical Guideline Centre. Clinical Guideline 114. Anaemia management in people with chronic kidney disease: full guidance. Feb 2011. Available at: http://www.nice.org.uk/nicemedia/live/13329/52851/52851.pdf. Accessed Jan 2013.

4 National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. *Am J Kidney Dis* 2006; 47 (5 Suppl 3): S11-145.

5 de Lusignan S, Chan T, Stevens P et al. Identifying patients with chronic kidney disease from general practice computer records. *Fam Pract* 2005; 22 (3): 234-41.

6 European Medicines Agency. CHMP assessment report: Rienso®. Procedure No.: EMEA/H/C/002215. Jul 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002215/WC500129751.pdf. Accessed Jan 2013.

7 National Institute for Health and Clinical Excellence. Clinical Guideline 114. Anaemia management in people with chronic kidney disease. Feb 2011. Available at: http://guidance.nice.org.uk/CG114. Accessed Jan 2013.

8 Kidney Disease: Improving Global Outcomes. KDIGO clinical practice guideline for anemia in chronic kidney disease. 2012. Available at: http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO-Anemia%20GL.pdf. Accessed Jan 2013.

9 Locatelli F, Aljama P, Barany P et al. Revised European best practice guidelines for the management of anaemia in patients with chronic renal failure. *Nephrol Dial Transplant* 2004; 19 Suppl 2: ii1-47.

10 All Wales Medicines Strategy Group. Final Appraisal Recommendation. Advice no. 1011. Ferric carboxymaltose (Ferinject®). Jul 2011. Available at: http://www.wales.nhs.uk/sites3/Documents/371/Ferric%20carboxymaltose%28ferinject%29%20FAR.pdf. Accessed Jan 2013.

11 Schiller B, Bhat P, Sharma A et al. Poster: Efficacy of Feraheme® (ferumoxytol) administration on target haemoglobin levels and other iron parameters across 3 dialysis chains. Presented at American Society of Nephrology Kidney week, Pensylvania, Phialdelphia, 8-13 November 2011. 11 Nov 2011.

12 AMAG Pharmaceuticals Inc. Clinical Study Report. Protocol No: FER-CKD-201. Ferumoxytol compared to iron sucrose trial (FIRST): a randomized, multicenter, trial of ferumoxytol compared to iron sucrose for the treatment of iron deficiency anemia in adult subjects with chronic kidney disease. Apr 2012.

13 Macdougall IC, McLaughlin J, Fortin GS et al. Poster: the FIRST head-to-head comparison study (Ferumoxytol compared to Iron Sucrose Trial) of the safety and efficacy of ferumoxytol compard with iron sucrose for the treatment of iron deficiency anaemia in patients with chronic kidney disease. Presented at American Society of Nephrology Kidney week, Pensylvania, Phialdelphia, 8-13 November 2011. 12 Nov 2011.

14 Provenzano R, Schiller B, Rao M et al. Ferumoxytol as an intravenous iron replacement therapy in hemodialysis patients. *Clin J Am Soc Nephrol* 2009; 4 (2): 386-93.

15 Spinowitz BS, Kausz AT, Baptista J et al. Ferumoxytol for treating iron deficiency anemia in CKD. *J Am Soc Nephrol* 2008; 19 (8): 1599-605.

16 AMAG Pharmaceuticals Inc. Clinical Study Report. Protocol No: 62,745-7. A phase III study of the safety and efficacy of ferumoxytol (compared with oral iron) as an iron replacement therapy in chronic kidney disease patients not on dialysis. Nov 2007.
17 Morgan A, Stradwick S. Systematic review of IV iron products in the treatment of iron deficiency anaemia in CKD. Mar 2011.
18 Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004; 23 (20): 3105-24.
19 Brereton N, Stradwick S, Freemantle N. Mixed treatment comparison: final report comparing ferumoxytol to alternative IV iron treatments. 2011.
20 Bailie GR. Comparison of rates of reported adverse events associated with i.v. iron products in the United States. *Am J Health Syst Pharm* 2012; 69 (4): 310-20.
21 Wysowski DK, Swartz L, Borders-Hemphill BV et al. Use of parenteral iron products and serious anaphylactic-type reactions. *Am J Hematol* 2010; 85 (9): 650-4.
22 Auerbach M, Kane RC. Caution in making inferences from FDA's Adverse Event Reporting System. *Am J Health Syst Pharm* 2012; 69 (11): 922-3.
23 Stoves J, Inglis H, Newstead CG. A randomized study of oral vs intravenous iron supplementation in patients with progressive renal insufficiency treated with erythropoietin. *Nephrol Dial Transplant* 2001; 16 (5): 967-74.
24 Albaramki J, Hodson EM, Craig JC et al. Parenteral versus oral iron therapy for adults and children with chronic kidney disease. *Cochrane Database Syst Rev* 2012; 1: CD007857.
25 Pharmacosmos UK Ltd. CosmoFer®. Summary of Product Characteristics. Dec 2012. Available at: http://www.medicines.org.uk/EMC/medicine/14139/SPC/CosmoFer/. Accessed Jan 2013.
26 Vifor Pharma UK Ltd. Venofer®. Summary of Product Characteristics. Mar 2011. Available at: http://www.medicines.org.uk/EMC/medicine/24168/SPC/Venofer+%28iron+sucrose%29/. Accessed Jan 2013.
27 Vifor Pharma UK Ltd. Ferinject®▼. Summary of Product Characteristics. Oct 2011. Available at: http://www.medicines.org.uk/EMC/medicine/24167/SPC/Ferinject+%28ferric+carboxymaltose%29/. Accessed Jan 2013.
28 Pharmacosmos UK Ltd. Monofer®▼. Summary of Product Characteristics. Jan 2013. Available at: http://www.medicines.org.uk/EMC/medicine/23669/SPC/Monofer+100mg+ml+solution+for+injection+infusion/. Accessed Jan 2013.
29 British Medical Association, Royal Pharmaceutical Society of Great Britain. *British National Formulary. No. 64.* Oct 2012.
30 Haymarket Publications. Monthly Index of Medical Specialities (MIMS). Sep 2012. Available at: http://www.mims.co.uk/. Accessed Jan 2013.
31 Bhandari S. Update of a comparative analysis of cost minimization following the introduction of newly available intravenous iron therapies in hospital practice. *Ther Clin Risk Manag* 2011; 7: 501-9.
32 Vicarey Davidson. Single use disposable instruments & infection control brochure 2009. 2009. Available at: http://www.vicareydavidson.com/Single_Use_Infection_Control_Brochure.pdf. Accessed Jan 2013.
33 Personal Social Services Research Unit. Unit Costs of Health and Social Care. 2010. Available at: http://www.pssru.ac.uk/project-pages/unit-costs/2010/index.php. Accessed Jan 2013.
34 Information Services Division Scotland, NHS Scotland. Scottish Health Service Costs: year ended 31 March 2011. Nov 2011. Available at:

http://www.isdscotland.org/Health-Topics/Finance/Publications/2011-11-29/2011-11-29-Costs-Report.pdf. Accessed Jan 2013.
35 National Institute for Health and Clinical Excellence, National Clinical Guideline Centre. Clinical Guideline 114. Anaemia management in people with chronic kidney disease: costing report. Implementing NICE guidance in England. Feb 2011. Available at: http://www.nice.org.uk/nicemedia/live/13329/52932/52932.pdf. Accessed Mar 2013.
36 StatsWales. 2013. Available at: www.statswales.wales.gov.uk. Accessed Feb 2013.
37 The Renal Association. UK Renal Registry. The fourteenth annual report 2011. Dec 2011. Available at: http://www.renalreg.com/Reports/2011.html. Accessed Jan 2013.
38 Levin A, Djurdjev O, Duncan J et al. Haemoglobin at time of referral prior to dialysis predicts survival: an association of haemoglobin with long-term outcomes. *Nephrol Dial Transplant* 2006; 21 (2): 370-7.
39 Keith DS, Nichols GA, Gullion CM et al. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 2004; 164 (6): 659-63.
40 Vifor Pharma UK Ltd. Ferinject®▼. Summary of Product Characteristics. Oct 2011. Available at: http://www.medicines.org.uk/EMC/medicine/24167/SPC/Ferinject+%28ferric+carboxymaltose%29/. Accessed Jan 2013.
41 Qunibi WY, Martinez C, Smith M et al. A randomized controlled trial comparing intravenous ferric carboxymaltose with oral iron for treatment of iron deficiency anaemia of non-dialysis-dependent chronic kidney disease patients. *Nephrol Dial Transplant* 2011; 26 (5): 1599-607.
42 Charytan C, Qunibi W, Bailie GR. Comparison of intravenous iron sucrose to oral iron in the treatment of anemic patients with chronic kidney disease not on dialysis. *Nephron Clin Pract* 2005; 100 (3): c55-c62.
43 Li H, Wang SX. Intravenous iron sucrose in peritoneal dialysis patients with renal anemia. *Perit Dial Int* 2008; 28 (2): 149-54.
44 Li H, Wang SX. Intravenous iron sucrose in Chinese hemodialysis patients with renal anemia. *Blood Purif* 2008; 26 (2): 151-6.
45 Li H, Wang SX. [Intravenous iron sucrose in maintenance dialysis patients with renal anemia: a clinical study]. *Zhonghua Yi Xue Za Zhi* 2009; 89 (7): 457-62.
46 Van Wyck DB, Roppolo M, Martinez CO et al. A randomized, controlled trial comparing IV iron sucrose to oral iron in anemic patients with nondialysis-dependent CKD. *Kidney Int* 2005; 68 (6): 2846-56.
47 Aggarwal HK, Nand N, Singh S et al. Comparison of oral versus intravenous iron therapy in predialysis patients of chronic renal failure receiving recombinant human erythropoietin. *J Assoc Physicians India* 2003; 51: 170-4.
48 Macdougall IC, Tucker B, Thompson J et al. A randomized controlled study of iron supplementation in patients treated with erythropoietin. *Kidney Int* 1996; 50 (5): 1694-9.
49 Winney RJ, Swainson CP, Parker AC et al. Oral or parenteral iron therapy in haemodialysis patients? *Proc Eur Dial Transplant Assoc* 1977; 14: 184-91.
50 Yan L, Wang M, Pan JS et al. Intravenous iron dextran treatment in chronic hemodialysis. *Chinese Journal of Nephrology* 2003; 19: 85-9.
51 Fudin R, Jaichenko J, Shostak A et al. Correction of uremic iron deficiency anemia in hemodialyzed patients: a prospective study. *Nephron* 1998; 79 (3): 299-305.
52 Agarwal R, Rizkala AR, Bastani B et al. A randomized controlled trial of oral versus intravenous iron in chronic kidney disease. *Am J Nephrol* 2006; 26 (5): 445-54.

53 Sheashaa H, El-Husseini A, Sabry A et al. Parenteral iron therapy in treatment of anemia in end-stage renal disease patients: a comparative study between iron saccharate and gluconate. *Nephron Clin Pract* 2005; 99 (4): c97-101.
54 Tsuchida A, Paudyal B, Paudyal P et al. Effectiveness of oral iron to manage anemia in long-term hemodialysis patients with the use of ultrapure dialysate. *Exp Ther Med* 2010; 1 (5): 777-81.

Appendix 1. Additional clinical information

Table 1A. Studies included in the mixed treatment comparison.

Study	Study design	Main inclusion criteria	Treatment groups	Primary endpoint	MTC endpoint
Ferumoxytol (Rienso®▼) versus oral iron					
Provenzano et al, 2009 (study 62,745-5)[14]	Multicentre, open-label, phase III RCT conducted over 35 days in ITT population	• Patients aged ≥ 18 years on haemodialysis (HD) for at least 90 days • Hb ≤ 11.5 g/dl • TSAT ≤ 30% • Serum ferritin ≤ 600 nanograms/ml • Stable (± 25%) dose ESA therapy for at least 10 days before dosing, remaining constant during the study	Ferumoxytol (n = 114): two 510 mg IV injections within 5 ± 3 days. Cumulative dose: 1.02 g Oral iron (n = 116): 200 mg daily for 21 days Cumulative dose: 4.2 g	Mean change in Hb levels from baseline to day 35: Ferumoxytol: 1.02 g/dl Oral iron: 0.46 g/dl p = 0.0002	
Spinowitz et al, 2008 (study 62,745-6)[15]	Multicentre, open-label, phase III RCT conducted over 35 days in ITT population	• Anaemic adult patients (≥ 18 years) with CKD stages 1–5 • Hb ≤ 11.0 g/dl • Serum ferritin ≤ 600 nanograms/ml • TSAT ≤ 30% • Patients were excluded where serum parathyroid hormone > 1500 nanograms/l	Ferumoxytol (n = 226): two 510 mg IV injections within 5 ± 3 days. Cumulative dose: 1.02 g Oral iron (n = 77): two 50 mg tablets twice daily starting at day 0 until day 21 Cumulative dose: 4.2 g	Mean change in Hb levels from baseline to day 35: Ferumoxytol: 0.82 g/dl Oral iron: 0.16 g/dl p < 0.0001	
Study 62,745-7[16]	Multicentre, open-label, phase III RCT conducted over 35 days in ITT population	• CKD patients aged ≥ 18 years • Patients on EPO must have received stable therapy for at least 10 (± 4) days prior to dosing and be expected to remain on a stable dose during study • Hb ≤ 11.0 g/dl at day 10 (± 4 days) and day 5 (± 3 days) • TSAT ≤ 30% and serum ferritin ≤ 600 nanograms/ml within 5 days (± 3 days) prior to dosing	Ferumoxytol (n = 226): two 510 mg IV injections within 5 ± 3 days. Cumulative dose: 1.02 g Oral iron (n = 77): two 50 mg tablets twice daily starting at day 0 until day 21 Cumulative dose: 4.2 g	Mean change in Hb levels from baseline to day 35: Ferumoxytol: 1.22 g/dl Oral iron: 0.52 g/dl p < 0.0001	
Ferric carboxymaltose (Ferinject®▼) versus oral iron					
Qunibi et al, 2011[41]	Multicentre, open-label, phase III RCT conducted over 56 days in ITT population	• Subjects ≥ 12 years of age • eGFR ≤ 45 ml/min/1.73 m^2 • Hb level ≤ 11 g/dl • TSAT ≤ 25% • Ferritin ≤ 300 nanograms/ml • If receiving ESA, dose must be fixed for ≥ 8 weeks prior to study enrolment	Ferric carboxymaltose (n = 144): 1000 mg IV infusion over 15 minutes (with up to two additional doses of 500 mg at two-week intervals). Oral iron (n = 101): 325 mg three times daily for 56 days.	Subjects achieving an increase in Hb of ≥ 1.0 g/dl between baseline and end of study: Ferric carboxymaltose: 60.4% Oral iron: 34.7% p < 0.001	Secondary endpoint: mean increase in Hb from baseline to week 8 Ferric carboxymaltose: 1.05 g/dl Oral iron: 0.70 g/dl p = 0.034

Study	Study design	Main inclusion criteria	Treatment groups	Primary endpoint	MTC endpoint
Iron sucrose (Venofer®) versus oral iron					
Charytan et al, 2005[42]	Multicentre, open-label, phase II/III RCT conducted over 43 days	• Nondialysis (ND) CKD patients (≥ 18 years) • Creatinine clearance of ≤ 40 ml/min • Hb < 10.5 g/dl • TSAT < 25% • Serum ferritin < 300 nanograms/ml • No other causes of anaemia	Iron sucrose (n = 48): 200 mg administered IV over five minutes on days 1, 8, 15, 22 and 29. Oral iron (n = 48): 325 mg tablets three times daily over 29 days.	Co-primary endpoint: Mean change from baseline to day 43 in Hb levels: Iron sucrose: 1.0 g/dl Oral iron: 0.7 g/dl p value: NS	
Li et al, 2008[43]	Single-centre, parallel-group RCT conducted over 56 days, in China in ITT population	• Receiving maintenance peritoneal dialysis (PD) • Stable condition for at least one month • Serum ferritin: < 500 nanograms/ml • TSAT < 30% • Hb: 60–90 g/l • Haematocrit: 18%–27%. • Patients were excluded where serum high-sensitivity C-reactive protein (hs-CRP) level ≥ 20 mg/l	Iron sucrose (n = 26): 200 mg IV infusion over at least 30 minutes, once weekly for the first four weeks and then once every other week. Oral iron (n = 20): 200 mg three times daily, for eight weeks.	Response rate (defined as Hb increase ≥ 15 g/l or haematocrit increase ≥ 5%) Iron sucrose: 94.8% Oral iron: 55.0% p < 0.05	Mean increase in Hb from baseline to week 8 Iron sucrose: 34.1% (33.8 g/l) Oral iron: 22.1% (17.7 g/l) p < 0.05
Li et al 2008[44]	Single-centre, parallel-group RCT conducted over 84 days, in China in ITT population	• Receiving maintenance HD, 2–3 times/week • Stable condition for at least one month • Serum ferritin: < 500 nanograms/ml • TSAT < 30% • Hb: 60–90 g/l • Haematocrit: 18%–27%. • Patients were excluded with hs-CRP level ≥ 20 mg/l	Iron sucrose (n = 70): 100 mg IV infusion over at least 30 minutes, twice weekly for the first eight weeks and then once weekly. Oral iron (n = 66): 200 mg three times daily for 12 weeks.	Response rate (full response: increase in Hb ≥ 30 g/l (or reaching 100 g/l) or haematocrit ≥ 10% (or reaching 33%) Partial response: Hb increase ≥ 15 g/l to < 30 g/l, or haematocrit ≥ 5% to < 10%). Iron sucrose: 88.6% Oral iron: 44.0% p < 0.05	Mean increase in Hb from baseline to week 8 Iron sucrose: 24.1% (37.7 g/l) Oral iron: 12.1% (17.9 g/l) p < 0.05
Li et al 2009[45]	RCT conducted over 84 days in ITT population	• Maintenance dialysis • Hb: 60–100 g/l • Haematocrit: 18%–30%	Iron sucrose (n = 102): HD patients: 200 mg IV once a week for four weeks and then 100 mg once a week for a further eight weeks. PD patients: 200 mg once a week for four weeks and then 200 mg once every other week for a further eight weeks. Oral iron (n = 92): 200 mg three times per day for 12 weeks.	Not reported	Mean increase in Hb from baseline to week 12 Iron sucrose: 30.1% (24.7 g/l) Oral iron: 22.1% (17.8 g/l) p < 0.05

Study	Study design	Main inclusion criteria	Treatment groups	Primary endpoint	MTC endpoint
Stoves et al, 2001[23]	Prospective RCT for an average follow-up of 5.2 months. An ITT analysis was not performed.	• Patients with progressive renal insufficiency (defined as progressive deterioration in renal function with a serum creatinine of more than 250 micromol/l, not requiring dialysis) • Worsening anaemia (defined as progressive reduction in Hb concentration to < 11 g/dl, irrespective of gender)	Iron sucrose (n = 22): 300 mg infusion over two hours, repeated monthly. Oral iron (n = 23): 200 mg three times per day for 12 weeks. Patients also received an EPO dose, which was adjusted according to a pre-arranged protocol in order to achieve similar Hb outcomes in the two groups.	Serum ferritin at six months: Iron sucrose: 330 micrograms/l Oral iron: 95 micrgrams/l Final doses of erythropoietin: Iron sucrose: 41.6 units/kg/week Oral iron: 33.5 units/kg/week	Median change in Hb from baseline to six months: Iron sucrose: 2.6 g/dl Oral iron: 2.5 g/dl
Van Wyck et al, 2005[46]	Multicentre, open-label, phase III RCT conducted over 56 days. An ITT analysis was not performed.	• Patients with CKD stage 3–5 • Hb ≤ 11.0 g/dl • TSAT ≤ 25% • Ferritin ≤ 300 nanograms/ml • Either no ESA or no ESA dose change for eight weeks	Iron sucrose (n = 95): either two 500 mg IV infusions on days 1 and 14 or 200 mg IV injections on five different days from day 0 to day 14. Oral iron (n = 93): 325 mg three times per day for 56 days.	Percentage of patients with an increase in Hb ≥ 1.0 g/dl at any time between baseline and either the end of study or withdrawal: Iron sucrose: 44.3% Oral iron: 28.0% p = 0.0344	Secondary endpoint: mean change in Hb from baseline to day 42 Iron sucrose: 0.7 g/dl Oral iron: 0.4 g/dl p = 0.0298
Iron dextran (CosmoFer®) versus oral iron					
Aggarwal et al, 2003[47]	RCT conducted over 12 weeks in ITT population.	• Patients aged ≥ 15 years with established chronic renal failure and anaemia • Hb between 5-8 gm% and packed cell volume between 15–24%	Iron dextran (n = 20): 2 ml IV infusion over one hour twice each month. Oral iron (n = 20): 200 mg three times daily.	Not reported	Change in Hb from baseline to week 12: Iron dextran: 4.22 gm% Oral iron: 2.68 gm% p < 0.001
Macdougall et al, 1996[48]	Prospective RCT conducted over four months in ITT population.	• Patient with renal anaemia starting EPO therapy • Receiving regular HD or PD (stable for ≥ three months) • Patients approaching end-stage renal failure but who had not yet commenced renal replacement therapy • Hb concentration ≤ 8.5 g/dl on three successive occasions • Serum ferritin 100–800 microgram/l • No other cause for anaemia • Serum CRP < 10 mg/l	Iron dextran (n = 12): 5 ml IV infusion every two weeks. Oral iron (n = 13): 200 mg three times daily. No iron supplementation (n = 12)	The principal endpoints of the study included Hb response: Iron dextran: 4.6 g/dl Oral iron: 3.0 g/dl No iron: 2.6 g/dl p < 0.005 for iron dextran versus both comparators at 16 weeks	
Winney et al, 1977[49]	RCT conducted over 12 months.	• Patients undergoing HD Further inclusion and exclusion criteria not reported.	Iron dextran (n = 14): 1 ml IV weekly. Oral iron (n = 14): 320 mg once daily.	Not reported	Change in Hb from baseline to month 12: Iron dextran: 1.4 g/dl Oral iron: 1.6 g/dl p < 0.001

Study	Study design	Main inclusion criteria	Treatment groups	Primary endpoint	MTC endpoint
Yan et al, 2003[50]	Study design not reported in abstract. Conducted over 56 days. Analysis in ITT population.	• Patients on chronic HD Further inclusion and exclusion criteria not reported.	Iron dextran IV (n = 70): dose not reported in abstract. Oral iron (n = 66): dose not reported in abstract.	Not reported	Mean increase in Hb from baseline to week 8 Iron dextran: 25.5% (18.0 g/l) Oral iron: 12.0% (8.5 g/l)
Other					
Fudin et al, 1998[51]	Prospective RCT with follow-up of 12 months for control group and 26 months in patients that received iron supplements. An ITT analysis was not performed.	• Patients were iron-deficient uraemics starting haemodialysis	Iron sodium gluconate (n = 24): 62.5 mg IV infusion once per week. Oral iron (n = 12): 160 mg once daily. No iron supplementation (n = 12).	Not reported	Mean increase in Hb from baseline to 26 months: Iron sodium gluconate: 3.2 g/dl Oral iron: 0.6 g/dl (based on estimation from study graph)[1,17]
Agarwal et al, 2006[52]	Multicentre, open-label, RCT conducted over 43 days. An ITT analysis was not performed.	• Patients ≥ 18 years • eGFR: 10–59 ml/min/1.73 m^2 • Not expected to start on dialysis for at least 16 weeks • Hb < 12.0 g/dl • Serum ferritin <100 nanograms/ml and/or TSAT < 20% • Patients were excluded if they had used any investigational or erythropoietic agents	Sodium ferric gluconate (n = 24): 250 mg IV infusion over one hour on days 1, 8, 15 and 22. Oral iron (n = 12): 325 mg three times daily for six consecutive weeks.	Mean change in Hb from baseline to day 43 Sodium ferric gluconate: 0.4 g/dl Oral iron: 0.2 g/dl p value: NS	
Sheashaa et al, 2005[53]	RCT conducted over six months in ITT population.	• Adult patients with end-stage renal disease undergoing maintenance HD • Anaemic with Hb of < 9 g/dl • In the preceding six months, patients had not received either EPO	Iron saccharate (n = 22): 100 mg IV infusion over one hour twice weekly for two months and once weekly thereafter. Sodium ferric gluconate (n = 26): 62.5 mg IV infusion over one hour twice weekly for two months and once weekly thereafter.	Not reported	Mean increase in Hb from baseline to six months: Iron saccharate: 2.15 g/dl Sodium ferric gluconate: 2.24 g/dl p = 0.256
Tsuchida et al, 2010[54]	Prospective RCT conducted over six months in ITT population.	• Patients with anaemia and regular HD for more than six months	Cideferron (n = 12): 50 mg IV infusion once weekly. Oral iron (n = 11): 305 mg once daily.	Primary purpose of the study was management of anaemia.	Mean increase in Hb from baseline to end of study: Cideferron: 1.17 g/dl Oral iron: 0.94 g/dl p value: NS

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; EPO: erythropoietin; ESA: erythropoiesis-stimulating agent; Hb: haemoglobin; HD: haemodialysis; Hs-CRP: high-sensitivity C-reactive protein; ITT: intent-to-treat; IV: intravenous; ND: not receiving dialysis; NS: not significant; PD: peritoneal dialysis; RCT: randomised controlled trial; TSAT: transferrin saturation.