

National PBM Drug Monograph
Ferumoxytol (Feraheme™)
December 2009
VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA National PBM-MAP/VPE drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary

- **Description and Indication:** Ferumoxytol is a superparamagnetic iron oxide that is supplied as an intravenous (IV) iron preparation. It is FDA-indicated for the treatment of iron-deficiency anemia (IDA) in adult patients with chronic kidney disease (CKD) who may or may not be receiving hemodialysis (HD).
- **Physiochemical Properties:** Ferumoxytol possesses unique physiochemical properties that result in less free iron *in vitro* than other available IV iron preparations. Release of free iron in the extracellular space has been hypothesized to account for many of the uncommon but serious adverse events of IV iron therapy (e.g., hypotension, hypersensitivity reactions), as well as increases in oxidative stress and risk of infection via increased microbial growth.
- **Dosage and Administration:** Ferumoxytol is administered as an undiluted IV injection of two doses of 510 mg (17 mL) each given 3 to 8 days apart. Doses may be administered at a rate of up to 30 mg/sec (1 mL/sec); therefore, each dose can be administered as rapidly as 17 seconds. In contrast to other IV iron preparations, which typically require from eight to ten sessions of IV administration in CKD patients on HD and from two to ten sessions of IV administration in non-HD CKD patients to provide adequate iron doses for repletion, the recommended iron repletion dose of approximately one gram is achieved in two sessions with ferumoxytol in CKD patients regardless of HD status.
- **Efficacy:** Ferumoxytol was evaluated in three Phase III open-label, randomized clinical trials that used oral iron as a comparator agent. Two of the trials studied the efficacy and safety of ferumoxytol in CKD patients Stages 1 through 5 who were not on dialysis, while the third trial assessed efficacy and safety parameters of ferumoxytol in patients receiving HD. Ferumoxytol had a greater increase in mean hemoglobin at Day 35 than oral iron (0.82 to 1.22 g/dL versus 0.16 to 0.52 g/dL, respectively; $p < 0.001$ for all three trials). Transferrin saturation (TSAT) and serum ferritin also had a statistically significant greater increase in the ferumoxytol groups compared to the oral iron groups.
- **Safety:** Ferumoxytol is generally well-tolerated, with the most frequently reported adverse events being diarrhea, nausea, dizziness, hypotension, constipation, and peripheral edema. Data from the combined analysis of the three trials show that ferumoxytol has a decreased incidence of adverse events than the comparator agent, oral iron. Notable differences between the adverse event profiles of these two agents include a higher incidence of dizziness and hypotension and a lower incidence of gastrointestinal adverse events with ferumoxytol than with oral iron. Ferumoxytol was also compared to placebo in a double-blind, crossover safety study in CKD patients both receiving and not receiving dialysis. The overall incidence of adverse events following ferumoxytol treatment was 21.3% compared to 16.7% in the placebo

arm. The incidence of treatment-related adverse events was 5.2% for ferumoxytol and 4.5% for placebo. The most frequently reported treatment-related adverse events were dizziness and nausea. The incidence of serious adverse events was higher after ferumoxytol (2.9%) versus placebo (1.8%), and the incidence of treatment-related serious adverse events was identical between the two groups (0.1%).

- **Diagnostic Imaging:** Ferumoxytol may affect the diagnostic ability of magnetic resonance (MR) imaging for up to three months after administration. It is currently being investigated as a diagnostic imaging agent in MR imaging studies of central nervous system inflammation, brain neoplasms, breast cancer, lung cancer, prostate cancer, lymphomas, and peripheral arterial disease.
- **Warnings and Precautions:** Like other IV iron preparations, ferumoxytol may cause serious hypersensitivity reactions (e.g., anaphylaxis, anaphylactoid reactions) as well as other adverse events potentially associated with hypersensitivity (e.g., pruritis, rash, urticaria, wheezing) and hypotension, which may be serious. Patients who receive ferumoxytol should be observed following injection for signs and symptoms of hypersensitivity (for at least 30 minutes following injection) and hypotension. Personnel and therapies should be available for the treatment of hypersensitivity reactions. The prescribing information for sodium ferric gluconate and for iron sucrose do not contain these specific recommendations.
- **Contraindications:** Like other IV preparations, ferumoxytol is contraindicated in patients with evidence of iron overload or anemia not caused by iron deficiency.
- **Cost:** Assuming a total iron repletion dose of one gram, ferumoxytol is approximately \$563.00 per treatment course. This acquisition cost is more than sodium ferric gluconate, iron sucrose, or low molecular weight (LMW) iron dextran; however, these cost comparisons do not take into account administration, supplies, and staffing time costs.
- **Conclusions:** Based on the currently available evidence, ferumoxytol has demonstrated to be effective and generally well-tolerated in clinical trials of adult patients with IDA and CKD. Doses of ferumoxytol can be administered more rapidly and adequate iron repletion can be achieved in fewer sessions compared to other IV iron preparations. It is recommended that patients be monitored for hypotension after administration of ferumoxytol. Patients should also be monitored for at least 30 minutes after administration for hypersensitivity reactions; ferumoxytol should only be administered in facilities where personnel and therapy are available should such a reaction occur. Head-to-head trials of ferumoxytol and other IV iron preparations are needed to determine whether one product has a better safety profile when compared to another. Choice of a particular preparation should consider the following: patient-specific factors and co-existing medical conditions, risk of adverse events, a patient's experience with a particular preparation, cost, and facility-specific resources (e.g., nursing and pharmacy personnel, time, and workload versus drug cost). Specific patient populations or circumstances at a site may warrant consideration as preferred therapy (due to economic considerations or convenience); this should be determined on a case by case basis at the local level.

Introduction

Anemia is the most common complication of chronic kidney disease (CKD); it develops early in the course of CKD and is present in nearly all patients with CKD Stage 5 (glomerular filtration rate (GFR) < 15 mL/min/1.73 m² or on dialysis). Anemia in CKD is primarily caused by a decrease in the

production of erythropoietin by the kidneys, which is usually treated with erythropoiesis stimulating agents (ESAs). Additional factors contributing to the development of anemia in CKD are a decreased red blood cell life span, iron deficiency, and blood loss either from regular laboratory testing or with hemodialysis (HD). Iron deficiency is the primary cause of resistance to therapy with ESAs. Iron agents may serve as either primary therapy, particularly for CKD patients not on dialysis, or as adjuvant therapy to ESAs. As an adjuvant, iron agents prevent iron deficiency and serve to minimize the dose of ESAs needed to achieve target-range hemoglobin levels. Iron agents are available as either oral or intravenous (IV) preparations. Current guideline recommendations state that the preferred route of administration is IV in patients with CKD dependent on HD. In patients with CKD who are not dependent upon HD or who receive peritoneal dialysis (PD), the route of iron administration can be either IV or oral.^{1,2}

Maintenance of iron status treatment targets have been recommended to minimize the ESA dose required or, in patients not receiving ESA therapy, maximize the hemoglobin level and minimize the need to initiate ESA therapy. For patients with HD-dependent CKD, the following goals are recommended: serum ferritin > 200 ng/mL and either transferrin saturation (TSAT) > 20% or reticulocyte hemoglobin content (CHr) > 29 pg/cell. For patients with non-HD-dependent CKD (including patients receiving PD), the following goals are recommended: serum ferritin > 100 ng/mL and TSAT > 20%. There is currently insufficient evidence to recommend or support the routine administration of IV iron in most patients with serum ferritin levels > 500 ng/mL. These targets help to ensure both the safe and effective use of iron agents.²

Iron dextran, sodium ferric gluconate, and iron sucrose are IV iron preparations used in the treatment of iron-deficiency anemia (IDA) in CKD. These preparations typically require from eight to ten sessions of IV administration in CKD patients on hemodialysis and from two to ten sessions of IV administration in non-hemodialysis CKD patients to provide adequate iron doses for repletion.³⁻⁵ High molecular weight (HMW) iron dextran has been associated with an increased risk of major adverse drug events (e.g., anaphylactoid reactions, cardiac arrest, coma) compared with low molecular weight (LMW) iron dextran and other IV iron preparations⁶ and is not recommended for use in the VA. Ferumoxytol is a recently FDA-approved addition to the available IV iron preparations.⁷

The purposes of this monograph are to evaluate the available evidence of ferumoxytol with regard to safety, tolerability, efficacy, cost, and other pharmaceutical issues and provide comparisons to other presently available VA national formulary IV iron preparations that would be relevant to evaluating ferumoxytol for possible addition to the VA national formulary.

Pharmacology/Pharmacokinetics

Ferumoxytol is a superparamagnetic iron oxide that is coated with a polyglucose sorbitol carboxymethyether shell.⁷ It possesses unique physiochemical properties that result in lower free iron, isotonicity, and neutral pH; these properties may allow for more rapid injection and injection of higher doses compared to other IV iron preparations.^{8,9} The release of bioactive or free iron in the extracellular space has been hypothesized to account for many of the uncommon but serious adverse events of IV iron therapy (e.g., hypotension, hypersensitivity reactions), to increase the risk of infection via increased microbial growth, and to increase oxidative stress.¹⁰ Ferumoxytol injection is an aqueous colloidal product formulated with mannitol (44 mg/mL).⁷ Each mL contains 30 mg elemental iron.⁷

The carbohydrate shell helps to isolate the bioactive iron from plasma components until the iron-carbohydrate complex enters the reticuloendothelial system macrophages of the liver, spleen, and

bone marrow. Once in the macrophages, the iron is released within vesicles and either binds to ferritin and enters the intracellular storage iron pool or transfers to plasma transferrin for transport to erythroid precursor cells for incorporation into hemoglobin.⁷

Table 1 below compares selected pharmacokinetic and physiochemical parameters of ferumoxytol and the IV iron preparations currently on the VA National Formulary. Following Table 1, Table 2 compares the *in vitro* free iron characteristics of ferumoxytol and the IV iron preparations currently on the VA National Formulary.

Table 1: Pharmacokinetic/Physiochemical Parameters of Selected IV Iron Preparations

	Ferumoxytol^{7,11}	LMW Iron Dextran³	Sodium Ferric Gluconate⁴	Iron Sucrose⁵
Molecular Weight (kDa)	750	165	289-440	34-60
Elemental Iron per mL (mg)	30	50	12.5	20
t _½ (h)	15-15.8	5-20	0.85-1.45	6
C _{max} (mcg/mL)	206*	N/A	19	N/A
T _{max} (h)	0.32	N/A	0.12	N/A
AUC (mcg-h/mL)	N/A	N/A	17.5-35.6	N/A
V _D (L)	3.16	N/A	6	10.0 (non-steady state) 7.9 (steady state)
CL	69.1 mL/h	N/A	3.02-5.35 L/h	1.2 L/h
Dialyzable	No	No	No	No

*after one 510 mg dose

Table 2: *In Vitro* Free Iron Characteristics of Selected IV Iron Preparations¹⁰

	Ferumoxytol	LMW Iron Dextran	Sodium Ferric Gluconate	Iron Sucrose
Free Iron (mcg/mL)*	0.3	149	295	7.6
% Free Iron by Ultrafiltration	0.001	0.298	2.360	0.038

*iron complex concentration 2 mg/mL

FDA Approved Indication(s) and Off-Label Uses

Approved by the FDA on June 30, 2009, ferumoxytol is an IV iron preparation indicated for the treatment of IDA in adult patients with CKD. Patients need not be receiving HD.⁷

In comparison, the FDA-approved indications for the IV iron preparations currently on the VA National Formulary are listed in Table 3 on the next page.

Table 3: FDA-Approved Indications for VANF IV Iron Preparations

LMW Iron Dextran³	Sodium Ferric Gluconate⁴	Iron Sucrose⁵
Adult patients and pediatric patients age 4 months and older with documented iron deficiency in whom oral administration is unsatisfactory or impossible	IDA in adult patients and in pediatric patients age 6 years and older undergoing chronic HD who are receiving an ESA	Treatment of IDA in the following adult patients: non-dialysis dependent CKD (may or may not be receiving an ESA) or HD-/PD-dependent CKD receiving an ESA

Ferumoxytol is currently being investigated as a diagnostic imaging agent in magnetic resonance imaging studies of central nervous system inflammation, brain neoplasms, breast cancer, lung cancer, prostate cancer, lymphomas, and peripheral arterial disease. Most of these clinical trials are currently in recruitment stages.¹²

Current VA National Formulary Alternatives

LMW iron dextran, sodium ferric gluconate, and iron sucrose are IV iron preparations that are listed on the VA National Formulary.

Dosage and Administration

The recommended dosage of ferumoxytol is an initial 510 mg dose followed by a second 510 mg dose 3 to 8 days later to achieve the usual recommended iron repletion dose of 1000 mg. It can be administered as an undiluted IV injection delivered at a rate of up to 1 mL/sec (30 mg/sec); therefore, each dose of ferumoxytol can be administered in as short as 17 seconds. A test dose of ferumoxytol is not required. Hemoglobin, ferritin, iron, and TSAT should be monitored at least one month after the second ferumoxytol injection. Ferumoxytol may be readministered in patients with persistent or recurrent IDA; at least one month should separate readministrations.⁷

For patients receiving hemodialysis, ferumoxytol should only be administered once the blood pressure is stable and the patient has completed at least one hour of hemodialysis.

All patients should be observed for at least 30 minutes following injection for signs and symptoms of hypersensitivity. Ferumoxytol should be administered only when personnel and therapies are readily available for treatment of hypersensitivity reactions. Patients should also be monitored for signs and symptoms of hypotension since serious hypotensive episodes have been reported in clinical trials.⁷

After administration of ferumoxytol, magnetic resonance (MR) imaging studies should be avoided for up to three months since ferumoxytol may transiently affect the diagnostic ability of MR imaging (see *Precautions/Contraindications*).⁷

For comparison, the FDA-approved dosages and administrations for the IV iron preparations currently on the VA National Formulary are listed in Table 4 on the next page.

Table 4: FDA-Approved Dosages and Administrations for VANF IV Iron Preparations

	LMW Iron Dextran^{3†}	Sodium Ferric Gluconate^{4†}	Iron Sucrose^{5†}
ND-CKD	<p>Dose (mL) = 0.0442 (desired Hgb – observed Hgb) x IBW + (0.26 x IBW) (or use dosage table in the package insert)</p> <p>Administration: undiluted IV (or IM*); ≤ 50 mg (1 mL)/min</p> <p>MDD: ≤ 100 mg (2 mL) (undiluted)</p> <p>Assuming cumulative iron dose of 1000 mg: at least 10 sessions required[§]</p>	N/A	<p>Dose: 200 mg (10 mL)</p> <p>Administration: undiluted IV injection over 2 to 5 min on 5 different occasions over a 14-day period</p> <p>Limited experience with 500 mg diluted IV infusion over 3.5 to 4 hr on days 1 and 14</p>
HD-CKD	Same as ND-CKD	<p>Dose: 125 mg (10mL)</p> <p>Administration: undiluted IV injection over at least 10 min or diluted IV infusion over 1 hr</p> <p>Assuming cumulative iron dose of 1000 mg: 8 sessions required (sequential dialysis sessions)</p>	<p>Dose: 100 mg (5 mL)</p> <p>Administration: undiluted IV injection over 2 to 5 min or diluted IV infusion over at least 15 min</p> <p>Assuming cumulative iron dose of 1000 mg: 10 sessions required (sequential dialysis sessions)</p>
PD-CKD	Same as ND-CKD	N/A	<p>Dose and administration: three divided doses by diluted IV infusion over a 28-day period (two infusions of 300 mg over 1.5 hr 14 days apart followed by one 400 mg infusion over 2.5 hr 14 days later)</p> <p>Assuming cumulative iron dose of 1000 mg: 3 sessions required</p>
Test Dose	Strongly recommended (25 mg)	Optional	Optional
Observation after Injection	At least one hour after administration of test dose before giving remainder of dose	N/A	N/A

ND-CKD = non-dialysis-dependent CKD HD-CKD = hemodialysis-dependent CKD
 PD-CKD = peritoneal dialysis-dependent CKD MDD = maximum daily dose

†Dosing regimen information provided reflects FDA-approved recommendations; actual clinical practice may differ.

*IM administration has been associated with local complications (e.g., bleeding, tissue necrosis or atrophy, sarcoma formation) and unpredictable absorption and should be avoided. IV administration of LMW iron dextran is preferred.¹³

§2001 NKF-KDOQI guideline recommendations state that, particularly for ND-CKD, home HD, and PD patients, it is reasonable to infuse LMW iron dextran as a single diluted dose of 500 to 1000 mg over 1 hour in a clinic setting or dialysis setting to minimize the need for frequent clinic visits.¹⁴ However, such doses are associated with an increased incidence of adverse events, particularly myalgias and arthralgias.^{3,14}

Cancer- and Chemotherapy-Induced Anemia: National Comprehensive Cancer Network guideline recommendations¹⁵ state that the maximum doses per infusion for IV iron preparations are as follows:

- LMW iron dextran: a total dose infusion may be given over several hours, if the dose exceeds 1000 mg, the remaining dose may be given after 4 weeks if inadequate hemoglobin response (non-FDA approved administration)
- Sodium ferric gluconate: 250 mg (non-FDA approved indication and administration)
- Iron sucrose: 300 to 400 mg (non-FDA approved indication and administration)

Ferumoxytol is not labeled for and has not yet been studied in cancer- and chemotherapy-induced anemia.

Efficacy

Efficacy Measures

The efficacy of ferumoxytol versus oral iron has been studied in clinical trials.^{8,15,16} Oral iron is an established comparator agent that has been used to evaluate the efficacy of other IV iron preparations. However, current guideline recommendations state that the preferred route of administration is IV in patients with CKD dependent upon HD.² In patients with CKD who are not dependent upon HD or who receive PD, the route of iron administration can be either IV or oral.²

Primary Efficacy Endpoint^{8,16,17}

- Mean change from baseline in hemoglobin (Hgb) at Day 35

Secondary Efficacy Endpoints^{8,16,17}

- Percentage of patients with at least 1 g/dL increase in Hgb at Day 35
- Mean change from baseline in Hgb at Day 21
- Mean change from baseline in TSAT and serum ferritin at Days 21 and/or 35
- Mean change from baseline in serum iron, total iron binding capacity (TIBC), and CHr at Days 21 and 35 – 3rd study only¹⁷

Summary of efficacy findings^{8,16-18}

The efficacy of ferumoxytol was evaluated in three Phase III randomized, open-label, multicenter clinical trials. Two studies^{8,16} assessed the efficacy of ferumoxytol in non-dialysis dependent CKD patients, while a third study¹⁷ evaluated patients with CKD Stage 5 on HD. Subjects in the first two studies may or may not have been receiving an ESA, but all patients in the third trial were on stable doses of ESAs. ESA dosing was to remain stable for the duration of each study. Subjects received either two doses of 510 mg of ferumoxytol within 5 ± 3 days of each other or 200 mg/day of elemental iron orally for 21 days. Laboratory assessments were conducted at baseline, Day 21, and Day 35 for each trial.

In all three studies, ferumoxytol was found to have a statistically significant greater increase in hemoglobin, TSAT, and serum ferritin than oral iron, as well as a statistically significant greater percentage of patients with ≥ 1 g/dL increase in hemoglobin than oral iron at Day 35. Hemoglobin, TSAT, and serum ferritin changes from baseline to Day 35 are presented in Table 5 on the next page.

Table 5: Hemoglobin, TSAT, and Serum Ferritin Changes from Baseline to Day 35

Endpoint (Change from baseline at Day 35)	Study I ⁸ Non-Dialysis CKD		Study II ¹⁶ Non-Dialysis CKD		Study III ¹⁷ CKD on HD	
	Ferumoxytol N=226	Oral Iron N=77	Ferumoxytol N=228	Oral Iron N=76	Ferumoxytol N=114	Oral Iron N=116
Hgb (mean±SD, g/dL)	1.22 ± 1.25*	0.52 ± 0.98	0.82 ± 1.24*	0.16 ± 1.02	1.02 ± 1.13*	0.46 ± 1.06
TSAT (mean±SD, g/dL)	9.2 ± 9.4*	0.3 ± 4.7	9.8 ± 9.2*	1.3 ± 6.4	6.6 ± 12.6*	0.6 ± 8.3
Ferritin (mean±SD, ng/mL)	412.6 ± 248.0*†	4.3 ± 48.2†	381.7 ± 278.6*	6.9 ± 60.1	233.9 ± 207.0*	-59.2 ± 106.2

*p<0.001 †Change from Baseline at Day 21

There was an optional non-randomized readmission phase for those patients who remained anemic after the completion of the randomized phase, defined as hemoglobin ≤ 11.0 g/dL in the non-dialysis trials and ≤ 11.5 g/dL in the hemodialysis trial.¹⁸ Patients who had previously received either ferumoxytol or oral iron had an increase in hemoglobin at Day 35 after a second round of treatment with two doses of 510 mg of ferumoxytol. Hemoglobin changes during this readmission phase are presented in Table 6 below.

Table 6: Hemoglobin Changes after Retreatment with Two Doses of 510 mg of Ferumoxytol¹⁸

Hgb (g/dL)	Prior Treatment Group				Total	
	Ferumoxytol 2 x 510 mg		Oral Iron 200 mg/day		n	Mean ± SD
	n	Mean ± SD	n	Mean ± SD		
Retreatment Period Baseline	22	9.91 ± 0.83	40	9.95 ± 0.72	62	9.93 ± 0.75
Retreatment Period Day 35	21	10.45 ± 0.80	36	10.71 ± 0.96	57	10.61 ± 0.90
Mean Change from Retreatment Baseline to Day 35	22	0.55 ± 0.89	40	0.69 ± 0.80	62	0.64 ± 0.83

Ferumoxytol consistently had a positive effect on mean change in hemoglobin in both the presence and absence of ESA therapy. In pooled data from the two Phase III non-dialysis studies,^{8,16} ferumoxytol produced larger increases in hemoglobin than oral iron in subjects on ESA therapy as well as individuals not on ESA therapy. Furthermore, the increase in hemoglobin seen with ferumoxytol alone (in the absence of ESA therapy) was larger than the increase resulting from oral iron in the presence of ESA therapy.¹⁸ The mean changes in hemoglobin in the presence or absence of ESA therapy in patients not receiving dialysis are presented in Table 7 on the next page.

Table 7: Mean Change in Hemoglobin in the Presence or Absence of ESA Therapy in Non-Dialysis Patients¹⁸

	ESA (+)		ESA (-)	
	Ferumoxytol 2 x 510 mg N=170	Oral Iron 200 mg/day N=65	Ferumoxytol 2 x 510 mg N=266	Oral Iron 200 mg/day N=84
Change in Hgb from Baseline at Day 35 (g/dL) (Mean ± SD)	1.54 ± 1.46	0.64 ± 1.32	0.82 ± 1.06	0.21 ± 0.80
P-value for Treatment Difference	<0.0001		<0.0001	

For further details on the efficacy results of the clinical trials, refer to *Appendix: Clinical Trials* (page 18).

Adverse Events (Safety Data)

The safety of ferumoxytol was studied in patients with all stages of CKD including CKD Stage 5 patients on HD. Across the three randomized clinical trials, a total of 605 patients were exposed to two doses of 510 mg of ferumoxytol separated by 5 ± 3 days and 280 patients were exposed to 200mg/day of oral elemental iron for 21 days.⁷

Common Adverse Events

The most common adverse events reported by patients treated with ferumoxytol were diarrhea (4.0%), nausea (3.1%), dizziness (2.6%), hypotension (2.5%), constipation (2.1%), and peripheral edema (2.0%).⁷ All adverse events reported by at least 1% of patients receiving ferumoxytol, as well as adverse events reported with other IV iron preparations, are included in Table 8 below. Adverse events were listed in the package inserts of LMW iron dextran, sodium ferric gluconate, and iron sucrose using the following criteria: for LMW iron dextran, reported adverse events were listed without further details³; for sodium ferric gluconate, the most frequent adverse events reported in two multiple-dose studies in hemodialysis patients were listed⁴; and for iron sucrose, treatment-emergent adverse events reported by at least 2% of treated patients in the clinical trials in patients with HD-CKD, ND-CKD, or PD-CKD (whether or not related to iron sucrose administration) were listed⁵.

Table 8: Comparative Adverse Event Profiles of Ferumoxytol, Oral Iron, and VANF IV Iron Preparations

Adverse Event	Ferumoxytol 2 x 510 mg ⁷ N=605	Oral Iron ^{7,8} N=280	LMW Iron Dextran ³	Sodium Ferric Gluconate ⁴	Iron Sucrose ⁵		
					HD-CKD N=231	ND-CKD N=139	PD-CKD N=75
Diarrhea	4.0%	8.2%	Reported	NVD=35%	5.2%	7.2%	8.0%
Nausea	3.1%	7.5%	Reported	See diarrhea	14.7%	8.6%	5.3%
Dizziness	2.6%	1.8%	Reported	13%	6.5%	6.5%	1.3%
Hypotension	2.5%	0.4%	Reported	29%	39.4%	2.2%	2.7%
Constipation	2.1%	5.7%	NR	NR	1.3%	4.3%	4.0%
Peripheral edema	2.0%	3.2%	NR	Reported	2.6%	7.2%	5.3%
Headache	1.8%	2.1%	Reported	7%	12.6%	2.9%	4.0%
Edema	1.5%	1.4%	Reported	5%	0.4%	6.5%	0%
Vomiting	1.5%	5.0%	Reported	See diarrhea	9.1%	5.0%	8.0%

Abdominal pain	1.3%	1.4%	Reported	6%	3.5%	1.4%	4.0%
Chest pain	1.3%	0.7%	Reported	10%	6.1%	1.4%	2.7%
Cough	1.3%	1.4%	NR	6%	3.0%	2.2%	1.3%
Pruritis	1.2%	0.4%	Reported	6%	3.9%	2.2%	2.7%
Pyrexia	1.0%	0.7%	Reported	5%	3.0%	0.7%	1.3%
Back pain	1.0%	0%	Reported	Reported	2.2%	2.2%	1.3%
Muscle spasm/ cramps	1.0%	1.4%	Reported	25%	29.4%	0.7%	2.7%
Dyspnea	1.0%	1.1%	Reported	11%	3.5%	3.6%	1.3%
Rash	1.0%	0.4%	Reported	Reported	0.4%	1.4%	0%
Hypertension	1.0%	0.7%	Reported	13%	6.5%	6.5%	8.0%
Ear pain	NR	NR	NR	Reported	0%	2.2%	0%
Conjunctivitis	NR	NR	NR	Reported	0.4%	0%	2.7%
Dysgeusia	NR	NR	NR	NR	0.9%	7.9%	0%
Asthenia	NR	NR	Reported	7%	2.2%	0.7%	2.7%
Fatigue	NR	NR	NR	6%	1.7%	3.6%	0%
Injection site reactions	NR	NR	Reported	33%	0%	3.6%	0%
URI NOS	NR	NR	NR	6%	1.3%	0.7%	2.7%
Graft complication	NR	NR	NR	NR	9.5%	1.4%	0%
Cardiac murmur/ arrhythmias	NR	NR	Reported	NR	0.4%	2.2%	0%
FOBT positive	NR	NR	NR	Reported	0%	1.4%	2.7%
Glycemic changes	NR	NR	NR	Reported	0.4%	3.6%	4.0%
Arthralgia	NR	NR	Reported	Reported	3.5%	1.4%	4.0%
Pain in extremity	NR	NR	NR	NR	5.6%	4.3%	2.7%
Paresthesia	NR	NR	Reported	6%	NR	NR	NR
Syncope	NR	NR	Reported	6%	NR	NR	NR
Hyperkalemia	NR	NR	NR	6%	NR	NR	NR
Abnormal erythrocytes	NR	NR	NR	11%	NR	NR	NR
Seizures	NR	NR	Reported	NR	NR	NR	NR

HD-CKD = hemodialysis-dependent CKD ND-CKD = non-dialysis-dependent CKD

PD-CKD = peritoneal dialysis-dependent CKD NVD = nausea/vomiting/diarrhea

URI NOS = upper respiratory tract infection not otherwise specified FOBT = fecal occult blood test NR = not reported

Adverse events leading to the discontinuation of ferumoxytol that occurred in at least two patients included hypotension, infusion site swelling, increased serum ferritin level, chest pain, diarrhea, dizziness, ecchymosis, pruritis, chronic renal failure, and urticaria.⁷

Hypotension: Hypotension without associated signs of hypersensitivity has been reported in 33 patients receiving ferumoxytol. Hypotension began within 30 minutes of administration for 14 patients, between 30 to 60 minutes after administration for 4 patients, and more than 60 minutes after administration for 15 patients. Three treatment-related serious cases of hypotension, which included one characterized as an anaphylactoid reaction, were observed across all clinical trials; all events resolved on the same day of occurrence without sequelae.^{7,18} A comparison of the hypotension and hypersensitivity reactions reported for ferumoxytol and the IV iron preparations currently on the VA National Formulary is provided in Table 9 below.

Table 9: Hypotension and Hypersensitivity Reactions with Ferumoxytol and VANF IV Iron Preparations

	Ferumoxytol⁷	LMW Iron Dextran³	Sodium Ferric Gluconate⁴	Iron Sucrose⁵
Hypotension	Reported in 1.9% of subjects, including 3 patients with serious hypotensive reactions. Monitor for signs and symptoms of hypotension following administration.	Not Reported	Associated with IV iron therapy. Hypotension reactions are not associated with signs of hypersensitivity and have usually resolved within 1-2 hours. Successful treatment may consist of observation, or if symptomatic, volume expansion.	Associated with IV iron therapy, and may be related to rate of administration and total dose administered. Caution should be taken to administer according to recommended guidelines.
Hypersensitivity Reactions	Reported in 0.2% of subjects. Other adverse reactions potentially associated with hypersensitivity (e.g. pruritis, rash, urticaria, or wheezing) were reported in 3.7% of these subjects. Observe for signs and symptoms of hypersensitivity for <u>at least</u> 30 minutes following administration, with personnel and treatment available if necessary.	Anaphylaxis and other hypersensitivity reactions have been reported after uneventful test doses as well as therapeutic doses.	One case of life-threatening hypersensitivity was observed in 1,097 patients who received a single dose in a post-marketing safety study. Post-marketing spontaneous reports of life-threatening reactions have been reported.	Reported. No life-threatening hypersensitivity reactions were observed in clinical studies, but several cases of moderate reactions were observed. Post-marketing spontaneous reports of life-threatening reactions have been reported.

Infections: Because multiple bacteria species rely on iron as a growth factor, it has been hypothesized that IV iron may facilitate bacterial infections in CKD patients. No increased risk of infection-related adverse events was observed in studies of CKD patients following treatment with ferumoxytol (1.1%) compared with oral iron (2.4%).¹⁸

Laboratory Measurements, Vital Signs, and Electrocardiograms (ECGs): No clinically significant differences between ferumoxytol and oral iron have been observed for clinical laboratory results (with the exception of iron indices) and vital signs. Additionally, no clinically relevant impact of ferumoxytol on ECGs has been found. Mean temperature, heart rate, and respiratory rate were similar following ferumoxytol and placebo treatment. Both ferumoxytol and placebo were well-tolerated from a hemodynamic standpoint, regardless of HD status.¹⁸

Effects on Ferritin Levels: Serum ferritin was a secondary efficacy endpoint in all three Phase III clinical trials. Across these studies, the mean change from baseline in serum ferritin in the ferumoxytol group at Days 21 and 35 was significantly greater than in the oral iron treatment group ($p < 0.0001$). The effect of serum ferritin on the tolerability profile of ferumoxytol was not prospectively evaluated; however, a post-hoc analysis showed that there was no impact of high achieved ferritin levels on the adverse event profile of ferumoxytol in CKD patients.¹⁸

Deaths and Other Serious Adverse Events (Sentinel Events)

Five serious adverse events that were considered related to study treatment were observed across all clinical trials involving ferumoxytol. Three hypotensive episodes occurred after the administration of ferumoxytol, one of which was also characterized as an anaphylactoid reaction. One adverse event, gastritis, occurred following oral iron therapy. The final adverse event, petechiae, was reported after placebo treatment. All events resolved within the same day and without complications.⁸

A lower incidence of death was reported in the ferumoxytol group than compared to oral iron therapy (1.1% versus 2.8%); however, no deaths were deemed to be related to treatment.⁸

Tolerability

A Phase III, randomized, double-blind, placebo-controlled crossover safety study was conducted to compare a single IV dose of 510 mg of ferumoxytol versus saline placebo. Of 750 patients randomized and crossed over, 713 patients were treated with ferumoxytol and 711 patients were given placebo. The overall incidence of adverse events following ferumoxytol treatment was 21.3% and 16.7% in the placebo arm. The incidence of treatment-related adverse events was 5.2% for ferumoxytol and 4.5% for placebo. An adverse event was attributed to treatment if it occurred within seven days after each study drug administration. However, adverse events that occurred on the day of the second injection that could not be definitively assigned to a treatment were conservatively attributed to ferumoxytol at the conclusion of the study. The most frequently reported treatment-related adverse events were infusion or injection-site reactions, dizziness, nausea, pruritis, headache, and fatigue. The incidence of serious adverse events was higher after ferumoxytol (2.9%) versus placebo (1.8%), and the incidence of treatment-related serious adverse events was identical between the two groups at 0.1%.¹⁹

For further details on the safety results of the clinical trials, refer to *Appendix: Clinical Trials* (page 18).

Precautions/Contraindications

Warnings and Precautions

Hypersensitivity Reactions: Ferumoxytol may cause serious hypersensitivity reactions, including anaphylaxis and/or anaphylactoid reactions. In clinical studies, serious hypersensitivity reactions were reported in 0.2% of subjects receiving ferumoxytol. Other adverse events potentially associated with hypersensitivity (e.g., pruritis, rash, urticaria, or wheezing) were reported in 3.7% of these subjects. Of note, clinical trials^{16,17} typically excluded patients with multiple drug allergies/sensitivities. Patients should be observed for signs and symptoms of hypersensitivity for at least 30 minutes following ferumoxytol injection. Personnel and therapies for the treatment of hypersensitivity reactions should be readily available.⁷

Hypotension: In clinical studies, hypotension was reported in 1.9% of subjects, including three cases of serious hypotensive reactions. Patients should be monitored for signs and symptoms of hypotension following ferumoxytol administration.⁷

Iron Overload: Excessive parenteral iron therapy can lead to excess storage of iron with the possibility of iatrogenic hemosiderosis. Patients' hematologic response should be regularly monitored during parenteral iron therapy. Ferumoxytol is not to be administered to patients with iron overload (see *Contraindications*). It is important to note that in the 24 hours following administration of ferumoxytol, laboratory assays may overestimate serum iron and transferrin-bound iron by also measuring the iron in the ferumoxytol complex.⁷

MR Imaging: Ferumoxytol administration may transiently affect the diagnostic ability of MR imaging. Alteration of MR imaging studies may persist for up to 3 months following the last ferumoxytol dose with maximum alteration of vascular MR imaging anticipated to be evident for 1-2 days following ferumoxytol administration. If MR imaging is required within 3 months after ferumoxytol administration, the use of T1- or proton density-weighted MR pulse sequences is recommended to minimize ferumoxytol's effects.⁷

Pregnancy Category C: There are no studies of ferumoxytol in pregnant women. In animal studies, ferumoxytol caused decreased fetal weights and fetal malformations at maternally toxic doses of 13-15 times the human dose. Use ferumoxytol during pregnancy only if the potential benefit justifies the potential risk to the fetus.⁷

Nursing Mothers: It is unknown if ferumoxytol is present in human milk. Because of the potential for adverse events in nursing infants, a decision should be made whether to discontinue nursing or to avoid ferumoxytol. The importance of ferumoxytol to the mother and the known benefits of nursing should both be taken into account.⁷

Geriatric Use: In premarketing clinical trials, 330 patients \geq 65 years of age were treated with ferumoxytol with no overall differences in safety and efficacy observed between older and younger patients. However, greater sensitivity of older individuals cannot be ruled out and dose administration should be cautious, as this population has higher incidences of renal, hepatic, and cardiac dysfunctions and other comorbid conditions.⁷

Renal/Hepatic Impairment: The manufacturer does not describe any recommended dosage adjustments in patients with renal or hepatic impairment who are receiving ferumoxytol.⁷ Although no dosage adjustments for patients with hepatic impairment are currently described by the manufacturer, data on the use of ferumoxytol in these patients are not explicitly available and clinical judgment should be used if ferumoxytol is considered for a patient with significant hepatic impairment.

Hemodialysis: Ferumoxytol is not removed by hemodialysis and may be administered in patients receiving hemodialysis once the blood pressure is stable and the patient has completed at least one hour of hemodialysis.⁷

Contraindications

Ferumoxytol is contraindicated in patients with evidence of iron overload, known hypersensitivity to ferumoxytol or any of its components, and anemia not caused by iron deficiency.⁷

Look-Alike/Sound-Alike (LASA) Error Risk Potential

As part of a Joint Commission standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from four data sources (Lexi-Comp, First Databank, USP Online LASA Finder, and ISMP Confused Drug Name List), the drug names presented in Table 10 below may cause LASA confusion.

Table 10: LASA Analysis Results for Ferumoxytol

Drug Name	Lexi-Comp	First DataBank	USP	ISMP	Clinical Judgment
Ferumoxytol 30mg/mL inj soln	Ferric gluconate Iron dextran complex Iron sucrose	None	None	None	None
Feraheme™ 30mg/mL inj soln	None	None	None	None	Ferrlecit™

*Indicates error that resulted in harm (per USP) ^Indicates error that did not result in harm (per USP)

Drug Interactions

Oral Iron: Ferumoxytol may reduce the absorption of concomitantly administered oral iron preparations.⁷

ESAs: In clinical trials, no drug-drug interactions related to the concomitant administration of ferumoxytol and ESAs were noted.^{8,16,17}

No other drug-drug interaction studies with ferumoxytol have been conducted.

Acquisition Costs

The acquisition cost and cost per typical regimen per patient for ferumoxytol and the VANF IV iron preparations are presented in Table 11 on the next page.

Table 11: Acquisition Costs of Ferumoxytol and Comparators

Drug	Dose	Price per Unit* (\$)	Cost/Regimen/ Patient (\$)
Ferumoxytol 30mg/mL (17mL SDV)	510mg x 2 doses	281.7000	563.40
LMW Iron Dextran 50mg/mL (2mL SDV)	100mg x 10 doses	18.5430	185.43
Sodium Ferric Gluconate 12.5mg/mL (5mL ampule)	HD-CKD: 125mg x 8 doses	16.5200	264.32
Iron Sucrose 20mg/mL (5mL SDV)	ND-CKD: 200mg x 5 doses	27.8160	278.16
	HD-CKD: 100mg x 10 doses		278.16
	PD-CKD: 300mg x 2 doses plus 400mg x 1 dose		278.16

*VA prices current as of 09/01/09 per McKesson; refer to available VA pricing resources for updated information

SDV = single dose vial; prices as of 09/01/09

ND-CKD = non-dialysis-dependent CKD

HD-CKD = hemodialysis-dependent CKD

PD-CKD = peritoneal dialysis-dependent CKD

Pharmacoeconomic Analysis

There are currently no published pharmacoeconomic analyses evaluating ferumoxytol. A budget impact model is available in the manufacturer's dossier for ferumoxytol.⁸ The model incorporates costs of reimbursement for IV iron preparations and for professional time for administration as well as the share of patients on each IV iron preparation.⁸

Conclusions

Ferumoxytol is an IV iron preparation that is FDA-approved for the treatment of IDA in adult patients with CKD who may or may not be receiving HD. Ferumoxytol *in vitro* has less free iron than other IV iron preparations, which may result in an improved side effect profile due to decreased oxidative stress and a reduced risk of free-iron-like reactions (e.g., hypotension, hypersensitivity reactions). However, serious hypersensitivity reactions and adverse reactions potentially associated with hypersensitivity were reported in clinical trials evaluating ferumoxytol (0.2% and 3.7%, respectively). Of note, these reactions were seen in a population that excluded patients with multiple drug allergies (i.e., patients that may be at greater risk for hypersensitivity reactions). Head-to-head trials of ferumoxytol with other IV iron preparations are needed to determine whether one product has a better safety profile compared to another.

An advantage of ferumoxytol over other IV iron preparations is the convenient dosing regimen of two doses of 510 mg that can each be administered over a minimum of 17 seconds; however, patients should be observed for at least 30 minutes following injection for signs and symptoms of hypersensitivity and hypotension. LMW iron dextran, sodium ferric gluconate, and iron sucrose typically require a 2- to 10-minute undiluted IV injection or a 0.25- to 2.5-hour diluted IV infusion depending upon preparation and indication. Usual iron repletion doses of one gram are achieved with two doses of ferumoxytol, at least ten doses of LMW iron dextran, eight doses of sodium ferric gluconate, and five to ten doses of iron sucrose (depending upon indication and when administered as an undiluted IV injection). However, if a patient requires single doses of less than 510 mg elemental iron, ferumoxytol may not be an appropriate therapy choice and may result in wasted medication if used.

In Phase III clinical trials, the use of ferumoxytol for the treatment of IDA in patients with CKD resulted in greater increases in hemoglobin, TSAT, and serum ferritin than oral iron. Although no

head-to-head studies comparing IV iron preparations have been conducted, data from Phase III studies of ferumoxytol have shown a similar increase in hemoglobin concentration when compared to data for other IV iron preparations. Ferumoxytol is well-tolerated, with the most commonly reported adverse events being diarrhea, nausea, dizziness, hypotension, constipation, and peripheral edema. Ferumoxytol was also compared to placebo in a double-blind, crossover safety study in CKD patients on and not on dialysis. Overall, similar types of adverse events occurred more frequently in the ferumoxytol group when compared to placebo. Related serious adverse events were identical between the two groups at an incidence of 0.1%. Based on these data, ferumoxytol was determined to be generally well-tolerated. IV iron preparations as a class (ferumoxytol, iron sucrose, LMW iron dextran, and sodium ferric gluconate) share a similar adverse event profile, with some unique differences. LMW iron dextran carries a Boxed Warning for anaphylactoid reactions; sodium ferric gluconate has a higher incidence of chest pain, dyspnea, abnormal erythrocytes, and injection site reactions; and iron sucrose is more commonly associated with muscle spasms, cramps, and pain in the extremities.

Two of the clinical trials evaluating ferumoxytol studied a population with a majority of female patients, which may decrease generalizability to the VA population. However, the third trial studied a predominately African-American population, which allows for better extrapolation to the VA population. Mean age for all trials was approximately 60 to 65 years, which is also applicable to the VA population.

Unlike LMW iron dextran, ferumoxytol does not require a test dose to detect a possible anaphylactic reaction; however, monitoring for hypersensitivity reactions and hypotension as well as having personnel and therapies available for the treatment of hypersensitivity reactions are recommended for ferumoxytol. Sodium ferric gluconate and iron sucrose do not carry explicit recommendations for such monitoring or personnel/therapy availability; however, higher doses and faster infusion rates of administration of these preparations have resulted in a greater frequency of side effects.

In regard to drug costs per regimen, assuming a total iron repletion dose of one gram, ferumoxytol is approximately two times more expensive than sodium ferric gluconate and iron sucrose and three times more expensive than LMW iron dextran. These cost comparisons do not take into account administration, supplies, and staffing time costs.

Since ferumoxytol was recently approved by the FDA in June 2009, comprehensive post-marketing surveillance is not yet available. Post-marketing data analysis is more extensive with the other currently available IV iron preparations.

Based on the currently available evidence, ferumoxytol has demonstrated to be effective and generally well-tolerated for IV iron replacement for IDA in adult patients with CKD. Adequate iron doses for repletion can be achieved in fewer sessions with ferumoxytol and doses can be rapidly administered compared to other available IV iron preparations. However, these advantages may be offset by the recommended monitoring for at least 30 minutes after administration and higher acquisition cost. In addition, the comparative safety profile of ferumoxytol versus other IV iron preparations is unclear at this time. Choice of a particular preparation should consider the following: patient-specific factors and co-existing medical conditions, risk of adverse events, a patient's experience with a particular preparation, cost, and facility-specific resources (e.g., nursing and pharmacy personnel, time, and workload versus drug cost). Specific patient populations or circumstances at a site may warrant consideration as preferred therapy (due to economic considerations or convenience); this should be determined on a case by case basis at the local level.

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Appendix: Clinical Trials

A literature search was performed on PubMed/Medline (1966 to August 2009) using the search terms ferumoxytol and Feraheme. The search was limited to studies performed in humans and published in English language. Reference lists of review articles and the manufacturer’s AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included, as well as unpublished data deemed relevant to this review.

Citation	AMCP Formulary Submission Dossier: Feraheme™. A phase III study of the safety and efficacy of Feraheme (compared with oral iron) as an iron replacement therapy in chronic kidney disease patients not on dialysis. Lexington, MA: AMAG Pharmaceuticals Inc;2009.																						
Study Goals	To assess the safety and efficacy of ferumoxytol for the treatment of iron deficiency anemia in patients with CKD not on dialysis.																						
Methods	<p>Study Design Pre-screening period of up to 8 weeks, a 10-day screening/baseline period, a 5-week randomized study period, and optional retreatment phase.</p> <p><u>Primary Endpoint</u></p> <ul style="list-style-type: none"> • Mean change from baseline in Hgb at day 35 post-initial dose <p><u>Secondary Endpoints</u></p> <ul style="list-style-type: none"> • Percent of patients with a ≥ 1.0 g/dL increase in Hgb at day 35 • Mean change from baseline in ferritin at day 21 • Percent mean change from baseline in TSAT at day 35 • Safety parameters: adverse reactions, clinical laboratory tests (hematology, clinical chemistry, and iron panel), vital signs (blood pressure, heart rate, respiration rate, and temperature), and physical examinations <p><u>Randomization Phase</u></p> <ul style="list-style-type: none"> • Randomized 3:1 to 2 x 510 mg IV ferumoxytol or 200 mg/day oral iron • 510 mg IV ferumoxytol administered on day 0 and day 5 \pm 3 days • Oral iron group received 2 Ferro-Sequels tablets twice daily for 200 mg/day from day 0 through day 21 <p><u>Retreatment Phase</u></p> <ul style="list-style-type: none"> • 510 mg ferumoxytol on day 0 and again 5 \pm 3 days later • Clinical assessments were on the same schedule as the randomization phase 																						
Criteria	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • ≥ 18 years of age and diagnoses with CKD as per KDOQI guidelines • Hgb ≤ 11.0 g/dL, TSAT $\leq 30\%$, and serum ferritin of ≤ 600 ng/mL • Stable ESA dose therapy for at least 10 days prior to dosing and remain on a stable dose for the duration of the study 																						
Results	<p>Baseline Characteristics</p> <table border="1"> <thead> <tr> <th></th> <th>Ferumoxytol (N=226)</th> <th>Oral Iron (N=77)</th> <th>Retreatment (N=51)</th> </tr> </thead> <tbody> <tr> <td>Mean Age, years</td> <td>65.75</td> <td>67.58</td> <td>65.95</td> </tr> <tr> <td>Gender (M,F)</td> <td>42%, 58%</td> <td>37.7%, 62.3%</td> <td>Majority female</td> </tr> <tr> <td>Race (Caucasian, Black, Other)</td> <td>67.3%, 31.4%, 1.2%</td> <td>62.3%, 33.8%, 4.1%</td> <td>Majority Caucasian</td> </tr> <tr> <td>CKD Stage (1/2, 3, 4, 5, not obtained)</td> <td>1.3%, 37.6%, 47.3%, 11.1%, 2.7%</td> <td>1.3%, 39%, 53.2%, 5.2%, 1.3%</td> <td>2%, 54.9%, 37.3%, 3.9%, 0%</td> </tr> </tbody> </table>				Ferumoxytol (N=226)	Oral Iron (N=77)	Retreatment (N=51)	Mean Age, years	65.75	67.58	65.95	Gender (M,F)	42%, 58%	37.7%, 62.3%	Majority female	Race (Caucasian, Black, Other)	67.3%, 31.4%, 1.2%	62.3%, 33.8%, 4.1%	Majority Caucasian	CKD Stage (1/2, 3, 4, 5, not obtained)	1.3%, 37.6%, 47.3%, 11.1%, 2.7%	1.3%, 39%, 53.2%, 5.2%, 1.3%	2%, 54.9%, 37.3%, 3.9%, 0%
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<p># of Patients on ESA</p>	<p>95 patients</p>	<p>34 patients</p>	<p>N/A; previous exposures: ferumoxytol = 21, oral iron = 30</p>
<p>Primary Efficacy Endpoint</p>			
<p>Mean change from baseline in Hgb (g/dL) at day 35</p>			
<p>Randomized Phase</p>		<p>Retreatment Phase</p>	
<p>Ferumoxytol: 1.22 ± 1.25 g/dL</p>		<p>Previous exposure to ferumoxytol: 0.31 g/dL</p>	
<p>Oral iron: 0.52 ± 0.98 g/dL</p>		<p>Previous exposure to oral iron 1.08 g/dL</p>	
<p>Secondary Efficacy Endpoints</p>			
<p>Randomized Phase</p>			
<ul style="list-style-type: none"> • Percent of patients with a ≥1.0 g/dL increase in Hgb, (%) <ul style="list-style-type: none"> ○ Ferumoxytol: 51.8% ○ Oral iron: 19.5% ○ p-value: <0.0001 • Mean change from baseline in ferritin at day 21 (ng/mL), mean ± SD <ul style="list-style-type: none"> ○ Ferumoxytol: 412.58 ± 247.95 ng/dL ○ Oral iron: 4.26 ± 48.22 ng/dL ○ p-value: <0.0001 • Percent mean change in TSAT from baseline at day 35 (%), mean ± SD <ul style="list-style-type: none"> ○ Ferumoxytol: 9.20 ± 9.37% ○ Oral iron: 0.28 ± 4.65% ○ p-value: <0.0001 			
<p>Safety</p>			
<p>Randomized Phase</p>			
<ul style="list-style-type: none"> • Most frequently reported adverse events <ul style="list-style-type: none"> ○ Ferumoxytol: diarrhea (5%), hypotension (5%), nausea (4.5%), constipation (4.1%), and dizziness (3.2%) ○ Oral iron: diarrhea (8.1%), nausea (8.1%), vomiting (6.8%), urinary tract infection (5.4%), and constipation (4.1%) • Related serious adverse events <ul style="list-style-type: none"> ○ One episode of gastritis in the oral iron group was reported • Deaths <ul style="list-style-type: none"> ○ 8 deaths occurred during the randomization phase of the study – one prior to treatment, 4 in the ferumoxytol group, and 3 in the oral iron group ○ No deaths were considered study-related 			
<p>Retreatment Phase</p>			
<ul style="list-style-type: none"> • Adverse reactions: diarrhea (5.9%), nausea (5.9%), dysgeusia (3.9%), gout (3.9%), headache (3.9%), hypotension (3.9%), muscle spasms (3.9%), and urinary tract infection (3.9%) • Related serious adverse events: None • Deaths: None 			
<p>Conclusions</p>	<p>Two 510 mg injections of ferumoxytol resulted in a statistically significant increase in both the primary and secondary endpoints. Additionally, ferumoxytol was well-tolerated with lower incidences of adverse reactions and serious adverse events when compared to oral iron. Retreatment with ferumoxytol resulted in an additional increase in Hgb levels, regardless of initial treatment. Overall, the authors conclude that IV ferumoxytol 2 x 510 mg is well-tolerated and more effective than oral iron 200mg/day x 21 days at increasing baseline Hgb levels in patients with CKD stages 1-5.</p>		

<p>Critique</p>	<p>Limitations</p> <ul style="list-style-type: none"> • Unpublished trial with data presented in the manufacturer’s dossier; neither statistical analysis methods nor baseline Hgb values were specified • Open-label study • Small patient size and short duration may not have provided adequate power to establish complete safety profile and true incidence of adverse events. • Compared to oral iron and not an IV iron preparation • Larger proportion of patients receiving ESA in ferumoxytol group than oral iron group and therefore the change in Hgb may be at least partially attributed to the ESA rather than ferumoxytol alone • Short follow-up period of 35 days rather than the 3 months necessary to fully assess the change in Hgb • Majority of patients are female which may not extrapolate well to the national VA population
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Citation	Spinowitz BS, Kausz AT, Baptista J, Noble SD, Sothinathan R, Bernardo M, et al. Ferumoxytol for treating iron deficiency anemia in CKD. J Am Soc Nephrol 2008;19:1599-605.
Study Goals	To evaluate the safety and efficacy of ferumoxytol for the treatment of iron deficiency anemia in patients with CKD not on dialysis.
Methods	<p>Study Design Open-label, randomized, controlled, multicenter Phase III clinical trial. Prescreening period up to 8 weeks, 10-day screening period prior to dosing, 35-day randomization phase, and optional retreatment phase to assess safety and efficacy of administering two courses of two doses of ferumoxytol and Hgb response in patients who remain anemic despite previous treatment with oral iron.</p> <p><u>Primary Endpoint</u></p> <ul style="list-style-type: none"> • Mean change from baseline in Hgb at day 35 post-initial dose <p><u>Secondary Endpoints</u></p> <ul style="list-style-type: none"> • Percent of patients with a ≥ 1.0 g/dL increase in Hgb • Mean change from baseline in ferritin • Percent mean change from baseline in iron, TSAT, and ferritin • Safety parameters: adverse reactions, clinical laboratory tests, and vital signs <p><u>Randomization Phase</u></p> <ul style="list-style-type: none"> • Randomized 3:1 to 2 x 510 mg IV ferumoxytol or 200 mg/day oral iron • 510 mg IV ferumoxytol administered on day 0 and day 5 \pm 3 days • Oral iron group received 2 Ferro-Sequels tablets twice daily for 200 mg/day from day 0 through day 21 <p><u>Retreatment Phase</u></p> <ul style="list-style-type: none"> • Nonrandomized • 510 mg ferumoxytol on day 0 and again 5 \pm 3 days later • Clinical assessments were on the same schedule as the randomization phase <p><u>Safety</u></p> <ul style="list-style-type: none"> • Vital signs obtained on days 0, 7, 14, 21, and 35 of oral iron group • Vital signs obtained on days 5, 10, 20, 21, 30, 35, and 60 in the ferumoxytol group • Patients were additionally monitored for hypersensitivity and hypotension following administration of ferumoxytol <p>Data Analysis Statistical tests used to compare the two treatment groups included a two-sided, two-sample <i>t</i> test or χ^2 test. Efficacy analysis was conducted using intent-to-treat and stratified by ESA use.</p>
Criteria	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Patients ≥ 18 years of age with a diagnosis of CKD stages 1 through 5 • Hgb ≤ 11.0 g/dL, serum ferritin ≤ 600 ng/mL, and TSAT $\leq 30\%$ <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Pregnancy or breastfeeding • Causes of anemia other than iron deficiency • Malignancy, except nonmelanoma skin cancer or disease-free for ≥ 2 years post-curative therapy • Use of another investigational drug or device within 30 days • Recent iron therapy • Serum PTH > 1500 pg/mL

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Results	<p>Study Population</p> <ul style="list-style-type: none"> • Ferumoxytol N=228 • Oral iron N=76 • Safety analysis, N=292 (217 ferumoxytol and 75 oral iron) • Retreatment phase, N=62 (22 ferumoxytol and 40 oral iron) <p>Baseline Characteristics</p> <table border="1" data-bbox="396 606 1406 968"> <thead> <tr> <th></th> <th>Ferumoxytol</th> <th>Oral iron</th> </tr> </thead> <tbody> <tr> <td>Age, years (mean ± SD)</td> <td>65.1 ± 14.3</td> <td>63.7 ± 11.1</td> </tr> <tr> <td>Gender (M, F)</td> <td>41.2%, 58.8%</td> <td>31.6%, 68.4%</td> </tr> <tr> <td>Race (Caucasian, Black, Other)</td> <td>57%, 34.2%, 8.8%</td> <td>60.5%, 36.8%, 2.7%</td> </tr> <tr> <td>CKD Stage (1/2, 3, 4, 5, missing)</td> <td>1.7%, 36%, 46.9%, 13.6%, 1.8%</td> <td>2.6%, 39.5%, 47.4%, 10.5%, 0%</td> </tr> <tr> <td># of Patients on ESA</td> <td>36.4%</td> <td>43.4%</td> </tr> <tr> <td>Hgb, g/dL (mean ± SD)</td> <td>9.96 ± 0.69</td> <td>9.96 ± 0.78</td> </tr> <tr> <td>Ferritin, ng/dL (mean ± SD)</td> <td>146.1 ± 173.6</td> <td>143.5 ± 144.9</td> </tr> <tr> <td>TSAT, % (mean ± SD)</td> <td>11.3 ± 6.1</td> <td>10.1 ± 5.5</td> </tr> </tbody> </table> <p>Primary and Secondary Efficacy Endpoints</p> <table border="1" data-bbox="396 1031 1312 1423"> <thead> <tr> <th>Parameter (day 35 change from baseline)</th> <th>Ferumoxytol</th> <th>Oral Iron</th> <th>P-value</th> </tr> </thead> <tbody> <tr> <td>Hgb (g/dL, mean ± SD)</td> <td>0.82 ± 1.24</td> <td>0.16 ± 1.02</td> <td><0.0001</td> </tr> <tr> <td>Hgb ≥ 1 g/dL increase from baseline (%)</td> <td>39.0</td> <td>18.4</td> <td>0.0010</td> </tr> <tr> <td>Ferritin (ng/mL, mean ± SD)</td> <td>381.7 ± 278.6</td> <td>6.9 ± 60.1</td> <td><0.0001</td> </tr> <tr> <td>Serum iron (mcg/dL, mean ± SD)</td> <td>22.7 ± 24.3</td> <td>4.4 ± 19.2</td> <td><0.0001</td> </tr> <tr> <td>TSAT (%), mean ± SD)</td> <td>9.8 ± 9.2</td> <td>1.3 ± 6.4</td> <td><0.0001</td> </tr> </tbody> </table> <p>Retreatment Phase</p> <table border="1" data-bbox="440 1482 1373 1623"> <thead> <tr> <th></th> <th>Baseline Mean Hgb (g/dL)</th> <th>Mean Change in Hgb (g/dL)</th> </tr> </thead> <tbody> <tr> <td>Previous ferumoxytol (N=22)</td> <td>9.91</td> <td>0.55 ± 0.89</td> </tr> <tr> <td>Previous oral iron (N=40)</td> <td>9.95</td> <td>0.69 ± 0.80</td> </tr> </tbody> </table>		Ferumoxytol	Oral iron	Age, years (mean ± SD)	65.1 ± 14.3	63.7 ± 11.1	Gender (M, F)	41.2%, 58.8%	31.6%, 68.4%	Race (Caucasian, Black, Other)	57%, 34.2%, 8.8%	60.5%, 36.8%, 2.7%	CKD Stage (1/2, 3, 4, 5, missing)	1.7%, 36%, 46.9%, 13.6%, 1.8%	2.6%, 39.5%, 47.4%, 10.5%, 0%	# of Patients on ESA	36.4%	43.4%	Hgb, g/dL (mean ± SD)	9.96 ± 0.69	9.96 ± 0.78	Ferritin, ng/dL (mean ± SD)	146.1 ± 173.6	143.5 ± 144.9	TSAT, % (mean ± SD)	11.3 ± 6.1	10.1 ± 5.5	Parameter (day 35 change from baseline)	Ferumoxytol	Oral Iron	P-value	Hgb (g/dL, mean ± SD)	0.82 ± 1.24	0.16 ± 1.02	<0.0001	Hgb ≥ 1 g/dL increase from baseline (%)	39.0	18.4	0.0010	Ferritin (ng/mL, mean ± SD)	381.7 ± 278.6	6.9 ± 60.1	<0.0001	Serum iron (mcg/dL, mean ± SD)	22.7 ± 24.3	4.4 ± 19.2	<0.0001	TSAT (%), mean ± SD)	9.8 ± 9.2	1.3 ± 6.4	<0.0001		Baseline Mean Hgb (g/dL)	Mean Change in Hgb (g/dL)	Previous ferumoxytol (N=22)	9.91	0.55 ± 0.89	Previous oral iron (N=40)	9.95	0.69 ± 0.80
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	<p>Safety</p> <ul style="list-style-type: none"> • Treatment-related adverse events <ul style="list-style-type: none"> ○ <u>Ferumoxytol (10.6% reported)</u>: nausea (1.8%), dizziness (1.8%), diarrhea (1.4%), chills (0.9%), rash (0.9%), dysguesia (0.9%), injection-site swelling (0.9%), constipation (0.5%), and upper abdominal pain (0.5%) ○ <u>Oral iron (24.0% reported)</u>: nausea (4.0%), diarrhea (5.3%), chills (1.3%), rash (1.3%), constipation (8.0%), upper abdominal pain (4.0%), and vomiting (2.7%) • Related serious adverse events: None reported • Deaths: None reported
<p>Conclusions</p>	<p>The authors conclude that ferumoxytol given as 2 x 510 mg doses within 1 week is more effective than oral iron in raising Hgb in patients with CKD. They also state a more rapid correction of iron deficiency may explain the difference in Hgb between ferumoxytol and oral iron compared to other IV iron preparations. Furthermore, ferumoxytol iron replacement may decrease the need for ESA therapy; however, further studies are required. Finally, the authors conclude ferumoxytol is better tolerated and more convenient than other IV iron therapies.</p>
<p>Critique</p>	<p>Limitations</p> <ul style="list-style-type: none"> • Open-label study • Small patient size and short duration may not have provided adequate power to establish complete safety profile and true incidence of adverse events. • Comparator agent oral iron rather than IV iron preparation • Short follow-up period of 35 days rather than the 3 months required to fully assess the change in Hgb • Majority of patients are female which may not extrapolate well to the national VA population

Citation	Provenzano R, Schiller B, Rao M, Coyne D, Brenner L, Pereira B.J.G. Ferumoxytol as an intravenous iron replacement therapy in hemodialysis patients. Clin J Am Soc Nephrol 2009;4:386-93.
Study Goals	To evaluate the safety and efficacy of ferumoxytol compared with oral iron in patients on HD receiving a stable ESA regimen, and the factors that affect Hgb response to IV iron in the current era of anemia management.
Methods	<p>Study Design Randomized, controlled, open-label, multicenter Phase III clinical trial.</p> <p><u>Primary Endpoint</u></p> <ul style="list-style-type: none"> • The mean change in Hgb from baseline to day 35 <p><u>Secondary Endpoints</u></p> <ul style="list-style-type: none"> • Proportion of patients with a ≥ 1 g/dL increase in Hgb at day 35 • Change in Hgb at day 21 • Change in TSAT, serum ferritin, serum iron, TIBC, and CHr at day 21 and day 35 • Safety analysis: adverse event monitoring, vital sign assessments, and clinical laboratory monitoring <p><u>Randomization Phase</u></p> <ul style="list-style-type: none"> • Randomized 1:1 to 2 x 510 mg IV ferumoxytol or 200 mg/day oral iron • 510 mg IV ferumoxytol administered on day 0 and day 5 \pm 3 days • Oral iron group received 2 Ferro-Sequels tablets twice daily for 200 mg/day from day 0 through day 21 • Laboratory and clinical evaluations were conducted on days -10, -5, 21 and 35 <p><u>Retreatment Phase</u></p> <ul style="list-style-type: none"> • Nonrandomized group of patients who remained anemic post-randomized phase • 510 mg ferumoxytol on day 0 and again 5 \pm 3 days later • Clinical assessments were on the same schedule as the randomization phase <p>Data Analysis Efficacy analysis was conducted on intent-to-treat principles. Treatment differences were assessed using two-sided, two-sample t-test or χ^2 test. An analysis of covariance model was used to compare day 35 Hgb change treatment differences when adjusted for baseline Hgb, TSAT, and ferritin. Linear regression was used to examine the relationship between change in Hgb and baseline parameters specified above.</p>
Criteria	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Patients ≥ 18 years with CKD per KDOQI guidelines • On HD for at least 90 days • Hgb ≤ 11.5 g/dL, TSAT $\leq 30\%$, serum ferritin ≤ 600 ng/mL • Stable ($\pm 25\%$) dose ESA therapy x at least 10 days and expected to remain constant during the study <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Pregnancy or breastfeeding • Causes of anemia other than CKD • Use of another investigational drug or device within 30 days • Iron therapy within 10 days • Recent blood transfusion • Active infection • Allergy to iron products or multiple drug classes

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	<p>Safety</p> <ul style="list-style-type: none"> • 54 patients (49.1%) reported 121 adverse events in the ferumoxytol group, and 64 patients (56.6%) experienced 152 adverse events in the oral iron group • Two patients receiving ferumoxytol had a serious adverse event (hypotension) that was considered related to treatment, one each in randomization and readmission phases ; no episodes of treatment-related serious adverse events were reported in the oral iron group • One death occurred in the ferumoxytol group and there were 3 deaths in the oral iron group; none were considered to be related to treatment
<p>Conclusions</p>	<p>The authors conclude ferumoxytol is superior to oral iron in increasing Hgb levels as well as serum ferritin, TSAT, and CHr, even after adjusting for baseline value discrepancies. Ferumoxytol was well-tolerated and associated with fewer adverse events than oral iron therapy. The authors believe the safety profile of ferumoxytol may be attributed to its unique physiochemical profile when compared to other IV iron preparations. The authors also found that the increase in Hgb with ferumoxytol was inversely related to baseline Hgb, thus reassuring against concerns for increasing Hgb to inappropriately high values. Finally, the Hgb response to ferumoxytol was unrelated to the baseline TSAT levels up to 30%, which suggests patients with these characteristics may benefit from ferumoxytol treatment.</p>
<p>Critique</p>	<p>Strengths</p> <ul style="list-style-type: none"> • Patients included in the study allow for better extrapolation to the veteran population <p>Limitations</p> <ul style="list-style-type: none"> • Open-label study. • Small patient size and short duration may not have provided adequate power to establish complete safety profile and true incidence of adverse events. • Ferumoxytol was compared to oral iron rather than another IV iron preparation, which is the standard of care for dialysis patients