Formulary Drug Reviews

Ferric Carboxymaltose

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Generic Name:	Ferric Carboxymaltose
Proprietary Name:	Injectafer (American Regent)
Approval Rating:	5S
Therapeutic Class:	Iron, Parenteral
Similar Drugs:	Ferumoxytol, Iron Dextran, Iron Sucrose, Sodium Ferric Gluconate Complex
Sound- or Look-Alike Names:	Interferon

INDICATIONS

Ferric carboxymaltose received US Food and Drug Administration (FDA) approval for the treatment of iron deficiency anemia in adult patients who are intolerant of oral iron or have had an unsatisfactory response to oral iron and in adult patients with nondialysis-dependent chronic kidney disease (CKD).¹

Table 1 compares the FDA-approved indications for parenteral iron products.

CLINICAL PHARMACOLOGY

Ferric carboxymaltose is an iron (III)-hydroxide carbohydrate complex designed to mimic physiologic

ferritin. It is pH neutral (5 to 7) and has physiologic osmolality.^{1,2}

Ferric carboxymaltose does not contain dextran or modified dextran and does not react with dextran antibodies.²

Table 2 compares the available parental iron products.

PHARMACOKINETICS

Following intravenous (IV) administration of ferric carboxymaltose at single doses ranging from 100 to 1,000 mg, a rapid, dose-dependent increase in total serum iron was observed. Peak serum iron levels occurred within 0.3 to 1.2 hours. Mean maximum total serum iron levels were 36.9 mcg/mL following a 100 mg IV dose, 154.1 mcg/mL following a 500 mg IV dose, and 306.4 to 317.9 mcg/mL following a 1,000 mg IV dose.^{3,4}

Iron administered as ferric carboxymaltose is rapidly distributed to the bone marrow, liver, and spleen. Peak serum ferritin levels occurred at 48 to 120 hours post infusion.³ The volume of distribution is about 3 L.¹

Levels declined over 24 to 72 hours; total serum iron levels were below the limit of quantification in the majority of patients within 60 to 96 hours post dose.³ Ferric carboxymaltose has a terminal elimination half-life

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Table 1. US Food and Drug Administration (FDA)–approved indications for parenteral iron products^{1,30-34}

	Ferric carboxymaltose	Ferumoxytol	Iron dextran	Iron sucrose	Sodium ferric gluconate complex
Iron deficiency anemia in nondialysis-dependent CKD	X				
Iron deficiency anemia in CKD		X		X	
Hemodialysis-dependent CKD patients receiving erythropoietin					X
Iron deficiency in patients in whom oral administration is unsatisfactory or impossible	X		X		

Note: CKD = chronic kidney disease.

of 7.4 to 12.1 hours.^{1,3} Less than 0.1% of the administered dose is excreted in the urine.^{3,5}

COMPARATIVE EFFICACY

Indication: Iron Deficiency Anemia Associated With Chronic Kidney Disease

Guidelines

Guideline: KDIGO clinical practice guideline for anemia in chronic kidney diseases

Reference: Kidney Disease: Improving Global Outcomes Anemia Work Group, 2012⁶

Comments: For adult CKD patients with anemia who are not receiving iron therapy, the guidelines advise a trial of IV iron if an increase in hemoglobin concentration without starting erythropoiesis-stimulating agent (ESA) treatment is desired, total saturation of transferrin is no greater than 30%, and ferritin is no greater than 500 ng/mL. For adult CKD patients receiving ESA therapy who are not receiving iron supplementation, the guidelines advise a trial of IV iron if an increase in hemoglobin concentration or a decrease in ESA dose is desired, total saturation of transferrin is no greater than 30%, and ferritin is no greater than 500 ng/mL. Alternatively, a 1- to 3-month trial of oral iron may be appropriate for adult CKD patients who are not receiving dialysis. For pediatric CKD patients with anemia who are on hemodialysis and not receiving iron or ESA therapy, the guidelines recommend oral or IV iron when total saturation of transferrin is 20% or lower and ferritin is 100 ng/mL or lower. For pediatric CKD patients on hemodialysis who are receiving ESA therapy and not receiving iron, the guidelines recommend oral or IV iron to maintain total saturation of transferrin greater than 20% and ferritin greater than 100 ng/mL. Regarding administration of the initial IV iron dose, the guidelines recommend monitoring the patient for 60 minutes after an initial

iron dextran infusion and suggest monitoring for 60 minutes after initial administration of nondextran IV iron. The guidelines also recommend that IV iron be avoided in patients with active systemic infections.

Guideline: KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease

Reference: KDOQI, et al, 2006⁷

Comments: Kidney Disease Outcomes Quality Initiative guidelines strongly recommend IV administration as the preferred route of iron administration for CKD patients on hemodialysis; IV or oral administration is an option in CKD patients not on dialysis or CKD patients receiving peritoneal dialysis. In CKD patients on hemodialysis who are receiving ESA treatment, sufficient iron should be administered to maintain serum ferritin greater than 200 ng/mL, total saturation of transferrin greater than 20%, or reticulocyte hemoglobin greater than 29 pg/cell; sufficient iron should be administered to maintain serum ferritin greater than 100 ng/mL and total saturation of transferrin greater than 20% in CKD patients not receiving dialysis or in CKD patients receiving peritoneal dialysis. The guidelines acknowledge there are no adequately powered studies directly comparing different IV iron agents.

Studies

Drug: Ferric Carboxymaltose vs Iron Sucrose

Reference: Szczech LA, et al, 2011^{8,9}

Study Design: Randomized, open-label, multicenter, noninferiority study

Study Funding: Luitpold Pharmaceuticals

Patients: 2,584 CKD patients who did not require dialysis with hemoglobin of 11.5 g/dL or less and ferritin of 100 ng/mL or less or 300 ng/mL or less when transferrin saturation was 30% or less; mean age was

Table 2. Comparative pharmacology for the various iron complexes^{1,30-35}

	Ferric carboxymaltose (<i>Injectafer</i>)	Ferumoxytol (<i>Feraheme</i>)	Iron dextran (<i>Dexferrum</i>)	Iron dextran (<i>INFeD</i>)	Iron sucrose (<i>Venofer</i>)	Sodium ferric gluconate complex (<i>Ferrlecit</i>)
Complex	Iron (III)-hydroxide carbohydrate complex	Nonstoichiometric magnetite coated with polyglucose sorbitol carboxymethylether (carboxymethylated dextran)	Liquid complex of ferric oxyhydroxide and dextran, a polyglucose	Liquid complex of ferric oxyhydroxide and dextran, a polyglucose	Complex of polynuclear iron (III)-hydroxide in sucrose	Complex of sodium ferric gluconate in sucrose
Molecular weight	150,000 daltons	750,000 daltons	265,000 daltons	165,000 daltons	34,000 to 60,000 daltons	289,000 to 440,000 daltons (37,500 daltons by alternative method)
Classification	Type I	Type I	Type I	Type I	Type II	Type IV
Reactivity with transferrin	Low	Low	Low	Low	Medium	High
Half-life	7 to 12 hours	15 hours	9 to 87 hours	5 to 20 hours	6 hours	1 hour

67 years and 64% were female; 54% of patients were White, 26% were Black, and 18% were Hispanic; mean baseline hemoglobin was 10.3 g/dL.

Intervention: Ferric carboxymaltose 15 mg/kg as 2 doses 1 week apart (to a maximum of 750 mg per dose), or iron sucrose 1 g administered as 5 infusions of 200 mg.

Results:

Primary Endpoint(s):

- Change from baseline to highest hemoglobin during first 56 days: 1.1 g/dL with ferric carboxymaltose and 0.9 g/dL with iron sucrose (difference, 0.21 g/dL; 95% confidence interval [CI], 0.13 to 0.28).
- Composite of death, myocardial infarction, stroke, unstable angina, congestive heart failure, arrhythmia, or protocol-defined hypertensive or hypotensive events up to day 120: 13.7% with ferric carboxymaltose versus 12.1% with iron sucrose (difference not significant).

Secondary Endpoint(s):

- Protocol-defined hypertensive events: 7.5% with ferric carboxymaltose versus 4.4% with iron sucrose (difference, 3.1%; 95% CI, 1.2 to 5).
- Protocol-defined hypotensive events: 1.8% with ferric carboxymaltose versus 3.2% with iron sucrose (difference, -1.4%; 95% CI, -2.7 to -0.1).

Limitations: Results of this study have only been presented as a meeting abstract.

Reference: Schaefer RM, et al, 2008¹⁰

Study Design: Randomized, open-label, multicenter study

Study Funding: Not stated

Patients: 183 patients with CKD on hemodialysis and hemoglobin of 11.5 g/dL or less and serum transferrin saturation less than 20%, or serum ferritin less than 200 mcg/mL.

Intervention: Ferric carboxymaltose 200 mg as an IV push injection (97 patients) or iron sucrose 200 mg given IV over 10 minutes (86 patients) was administered 2 to 3 times weekly until the total cumulative dose for each patient was reached. Patients received ferric carboxymaltose or iron sucrose IV into the hemodialysis venous line 1 hour after the start of the dialysis session. The mean duration of treatment was 15.8 days in the ferric carboxymaltose group and 16.2 days in the iron sucrose group.

Results:

Primary Endpoint(s):

- Hemoglobin increase of at least 1 g/dL at week 4: 46.4% of patients with ferric carboxymaltose versus 37.2% of patients with iron sucrose.

Secondary Endpoint(s):

- Mean hemoglobin levels increased from 9.3 to 10.6 g/dL in the ferric carboxymaltose group and from 9.3 to 10.3 g/dL in the iron sucrose group.

- Serum ferritin levels increased from 90.4 to 723.4 mcg/L in the ferric carboxymaltose group and from 93.1 to 549.6 mcg/L in the iron sucrose group.

Limitations: Results of this study have only been presented as an abstract. Results were reported only for the per-protocol population.

Drug: Ferric Carboxymaltose vs Oral Iron

Reference: Qunibi WY, et al, 2011¹¹

Study Design: Randomized, open-label, multicenter study

Study Funding: American Regent

Patients: 255 nondialysis-dependent CKD patients with iron deficiency anemia, a glomerular filtration rate of 45 mL/min/1.73 m² or less, hemoglobin levels of 11 g/dL or less, transferrin saturation of 25% or less, and ferritin levels of 300 ng/mL or less. Those receiving an ESA had to be on a fixed stable dose for at least 8 weeks prior to study entry.

Intervention: Ferric carboxymaltose 15 mg/kg (up to 1,000 mg) IV over 15 minutes, with up to 2 additional 500 mg doses at 2-week intervals (152 patients), or ferrous sulfate 325 mg orally 3 times daily 1 hour before meals for a total elemental iron of 195 mg daily for 56 days (103 patients); mean cumulative dose was 1,218 mg in the ferric carboxymaltose group and 2,638 mg in the ferrous sulfate group.

Results:

Primary Endpoint(s):

- Hemoglobin level increase of at least 1 g/dL at any time from baseline to day 56: 60.4% of patients receiving ferric carboxymaltose and 34.7% of patients receiving oral iron ($P < .001$).

Secondary Endpoint(s):

- Clinical response (increase in hemoglobin of at least 1 g/dL and increase in ferritin of at least 160 ng/mL).
- Mean change in hemoglobin from baseline to day 42 and day 56: increased from 10.15 g/dL at baseline to 11.09 g/dL at day 42 and to 11.19 g/dL at day 56 in the ferric carboxymaltose group and from 10.03 g/dL at baseline to 10.53 g/dL at day 42 and to 10.75 g/dL at day 56 in the oral iron group ($P < .001$ for differences between groups at both time points).

Other Endpoint(s):

- Change in mean serum ferritin: increased from 111.9 ng/mL at baseline to 732.7 ng/mL at day 14 and to 471.5 ng/mL at day 56 in the ferric carboxymaltose group, and from 105.4 ng/mL at

baseline to 114 ng/mL at day 14 and to 137 ng/mL at day 56 in the oral iron group ($P < .001$ for difference at day 14 and day 56).

- Change in transferrin saturation: increased in both treatment groups, with no difference between groups at days 42 or 56.
- Treatment-related adverse events occurred in 2.7% of patients treated with ferric carboxymaltose compared with 26.2% treated with oral iron ($P < .001$), with the difference primarily driven by a higher incidence of constipation in the oral iron group.

Drug: Ferric Carboxymaltose vs IV Iron, Oral Iron, or No Iron (standard medical care)

Reference: Charytan C, et al, 2013¹²

Study Design: Randomized, open-label, multicenter study

Study Funding: Luitpold Pharmaceuticals

Patients: 513 patients with CKD and hemoglobin of 11.5 g/dL or less, transferrin saturation of 30% or less, and ferritin of 300 ng/dL or less if nondialysis-dependent (416 patients), or hemoglobin of 12.5 g/dL or less, transferrin saturation of 30% or less, and ferritin of 500 ng/mL or less if dialysis-dependent (97 patients); mean age was 63 years. Hemodialysis patients were only eligible if they did not anticipate needing repletion therapy (more than 200 mg of IV iron) during the 30-day study period.

Intervention: Ferric carboxymaltose 15 mg/kg to a maximum of 1,000 mg IV undiluted in patients with nondialysis-dependent CKD (204 patients; mean total dose, 975 mg) or 200 mg IV push undiluted 30 to 60 minutes into the dialysis session in patients with dialysis-dependent CKD (50 patients; mean total dose, 200 mg), or standard medical care as determined by the investigator, which included oral iron, IV iron, or no iron (212 patients with nondialysis-dependent CKD and 47 patients with dialysis-dependent CKD); in the standard medical care group, 62.9% received IV iron (mean dose, 699 mg in nondialysis patients and 561 mg in dialysis patients), predominantly iron sucrose (49%), while 30% received oral iron.

Results:

Primary Endpoint(s):

- Safety of the maximum administered dose of ferric carboxymaltose compared with standard medical care: adverse events occurred in 30.3% of patients in the ferric carboxymaltose group and 32.8% in the group receiving standard medical care. Serious

events occurred in 3.5% of patients in the ferric carboxymaltose group compared with 8.9% in the standard care group ($P < .02$).

Secondary Endpoint(s):

- Increase in hemoglobin of at least 1 g/dL at any time between baseline and day 30: 25.7% of patients in the ferric carboxymaltose group and 22.1% in the standard care group.
- Hemoglobin greater than 12 g/dL at any time between baseline and day 30: 14.5% of patients in the ferric carboxymaltose group and 12.9% in the standard care group.
- Mean change from baseline to day 30 for hemoglobin: 0.49 g/dL in the ferric carboxymaltose group and 0.33 g/dL in the standard care group ($P = .061$).
- Mean change from baseline to day 30 for ferritin: 242.58 ng/mL in the ferric carboxymaltose group and 103.17 ng/mL in the standard care group ($P \leq .001$).
- Mean change from baseline to day 30 for transferrin saturation: 8.61% in the ferric carboxymaltose group and 5.1% in the standard care group ($P \leq .001$).

Limitations: Efficacy endpoints were exploratory.

Drug: Ferric Carboxymaltose

Reference: Covic A, et al, 2010¹³

Study Design: Open-label, single-arm, multicenter study

Study Funding: Vifor International

Patients: 163 patients on hemodialysis with iron deficiency anemia.

Intervention: Ferric carboxymaltose 100 to 200 mg as an IV bolus push injection into the hemodialysis venous line 2 to 3 times weekly for no more than 6 weeks. Stable doses of an ESA were permitted throughout the study. The mean cumulative dose of iron as ferric carboxymaltose was 2,133 mg.

Results:

Primary Endpoint(s):

- Safety: Adverse events were reported in 54.6% of patients; treatment was discontinued because of an adverse event in 3.1% of patients.

Secondary Endpoint(s):

- Treatment response, defined as attainment of a 1 g/dL or greater increase in hemoglobin levels from baseline at any time during the study, was achieved in 100 patients in the intent-to-treat population (61.7%).
- Change in hemoglobin from baseline: increased from 9.1 g/dL at baseline to 10.3 g/dL at follow-

up. The mean change in hemoglobin levels 2 weeks after the first dose (after 4 to 6 doses) was 0.53 g/dL (95% CI, 0.4 to 0.67).

- Serum ferritin levels and transferrin saturation improved from suboptimal levels to within the target range within 2 weeks of the initial dose.

Comments: Experience with ferric carboxymaltose was also described in 30 consecutive adult predialysis patients with CKD from a single institution. Patients had hemoglobin levels of 11 g/dL or less and ferritin levels less than 300 ng/mL. All received a single dose of ferric carboxymaltose 800 mg infused over 15 minutes without a test dose. After 1 month, hemoglobin levels increased in 80% of patients, did not change in 3% of patients, and declined in 17% of patients. A hemoglobin level greater than 11 g/dL was achieved in 28.6% of patients at 2 weeks and 21.4% at 1 month. Mean hemoglobin levels increased by 0.53 g/dL after 2 weeks and by 0.73 g/dL after 1 month. Ferritin levels increased from 89.7 ng/mL at baseline to 526.3 ng/mL at 2 weeks and to 364.7 ng/mL at 1 month.¹⁴ Experience with ferric carboxymaltose was also described in 44 patients (17 with CKD and 27 kidney transplant recipients) with iron deficiency from another institution. A total of 46 doses were administered either as a single 100 or 200 mg injection (42 doses) or as a short infusion of up to 500 mg (4 doses). Small, insignificant increases in hemoglobin levels were observed (from 10.6 to 11 g/dL [$P = .557$] in the CKD group and from 11.3 to 11.7 g/dL [$P = .359$] in the transplant group). No serious adverse events were observed.¹⁵

Limitations: This was a single-arm, noncomparative study.

Indication: Iron Deficiency Anemia in Patients Intolerant of Oral Iron or Who Have Had an Unsatisfactory Response to Oral Iron, or Iron Deficiency Anemia Associated With Various Medical Conditions

Guidelines

Guideline: Guidelines for the Management of Iron Deficiency Anemia

Reference: Goddard AF, et al, 2011¹⁶

Comments: In patients with iron deficiency anemia, iron supplementation is necessary to correct anemia and replenish body stores. Parenteral iron is recommended when oral preparations are not tolerated or an adequate response is not achieved. The guidelines do not recommend one particular parenteral iron over others but do highlight the convenience of the

shorter infusion duration with ferric carboxymaltose and the good tolerability of iron sucrose, both relative to iron dextran.

Guideline: ACOG Practice Bulletin No. 95: Anemia in Pregnancy

Reference: American College of Obstetricians and Gynecologists, 2008¹⁷

Comments: The guidelines acknowledge that parenteral iron may be appropriate in pregnant patients who will not take modest doses of oral iron, patients not able to tolerate oral iron, patients with malabsorption syndrome, and patients with severe iron deficiency anemia. The guidelines do not recommend one particular parenteral iron over others but acknowledge the higher incidence of allergic reactions with iron dextran relative to iron sucrose.

Studies

Drug: Ferric Carboxymaltose vs IV Iron or Oral Iron

Reference: Onken JE, et al, 2013¹⁸

Study Design: Randomized, open-label, multicenter study

Study Funding: Luitpold Pharmaceuticals

Patients: 507 patients with iron deficiency anemia responding inadequately to 14 days of ferrous sulfate 325 mg orally 3 times daily (cohort 1), and 504 patients with iron deficiency anemia who were unable to tolerate oral iron or for whom oral iron was deemed inappropriate (cohort 2); patients had a screening hemoglobin of 11 g/dL or less, a ferritin level of 100 ng/mL or less or no greater than 300 ng/mL, and a transferrin saturation of 30% or less after 14 days of oral ferrous sulfate (325 mg 3 times daily).

Intervention: Patients in cohort 1 were assigned to therapy with 2 doses of ferric carboxymaltose 15 mg/kg (up to 750 mg) IV separated by 1 week (250 patients) or ferrous sulfate 325 mg orally 3 times daily for 14 additional days (257 patients); patients in cohort 2 were assigned to therapy with 2 doses of ferric carboxymaltose 15 mg/kg (up to 750 mg) IV separated by 1 week (253 patients) or other IV iron (251 patients; iron sucrose in 89.8%).

Results:

Primary Endpoint(s):

- Change from baseline to highest observed hemoglobin at any time between baseline and day 35 in cohort 1: 1.57 g/dL with ferric carboxymaltose and 0.8 g/dL with ferrous sulfate ($P = .001$).

Secondary Endpoint(s):

- Change from baseline to highest observed hemoglobin at any time between baseline and day 35 in cohort 2: 2.9 g/dL with ferric carboxymaltose and 2.16 g/dL with other IV iron ($P = .001$).
- Patients achieving a hemoglobin of at least 12 g/dL at any time between baseline and day 35: 57% with ferric carboxymaltose and 29.1% with ferrous sulfate in cohort 1 ($P = .001$), and 50.6% with ferric carboxymaltose and 24.5% with other IV iron in cohort 2 ($P = .001$).
- Change from baseline to highest ferritin measurement at any time between baseline and day 35: Results were not reported.
- Patients achieving a hemoglobin level of more than 12 g/dL and an increase in ferritin of at least 160 ng/mL at any time between baseline and day 35: Results were not provided, but were reported to be significantly greater in both ferric carboxymaltose groups than in the comparator groups.
- Patients achieving an increase in hemoglobin of at least 2 g/dL at any time between baseline and day 35: Results were not reported.
- Drug-related treatment-emergent adverse events: 22.8% of patients in the ferric carboxymaltose group and 6.3% in the ferrous sulfate group in cohort 1, and 25.3% of patients in the ferric carboxymaltose group and 26.5% in the other IV iron group in cohort 2.
- Treatment-emergent serious adverse events: 3.3% of patients in the ferric carboxymaltose group and 4% in the ferrous sulfate group in cohort 1, and 6.7% of patients in the ferric carboxymaltose group and 6.5% in the other IV iron group in cohort 2.
- Composite safety endpoint (all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, unstable angina, heart failure, arrhythmias, hypertensive events, or hypotensive events): 2.9% in the ferric carboxymaltose group and 1.6% in the ferrous sulfate group in cohort 1, and 4% in the ferric carboxymaltose group and 4.9% in the other IV iron group in cohort 2.

Limitations: Comparator treatment was selected at investigator discretion and was not standardized.

Reference: Barish CF, et al, 2012¹⁹

Study Design: Two randomized, open-label, multicenter studies

Study Funding: Luitpold Pharmaceuticals

Patients: 1,435 patients with iron deficiency anemia with hemoglobin of 12 g/dL or less, ferritin levels of

100 ng/mL or less or 300 ng/mL or less, and transferrin saturation of 30% or less.

Intervention: Ferric carboxymaltose 15 mg/kg (up to 750 mg) IV as a single dose (366 patients) or 15 mg/kg (up to 750 mg) IV weekly until the calculated iron deficit was administered (343 patients; maximum cumulative dose of 2,250 mg), or standard medical care (IV iron, oral iron, or no iron) from day 0 to 35 in the single-dose study (360 patients) or day 0 to 42 for the multidose study (366 patients).

Results:

Primary Endpoint(s):

- Safety of ferric carboxymaltose compared with standard medical care: In the single-dose study, treatment-emergent adverse events occurred in 36% of patients receiving ferric carboxymaltose and 34.6% receiving standard medical care. The most common events were nausea, vomiting, constipation, diarrhea, urinary tract infection, and abdominal pain in the standard medical care group and nausea, headache, diarrhea, and fatigue in the ferric carboxymaltose group. The most common treatment-emergent adverse events (incidence of at least 5%) in the multidose study were nausea, constipation, dizziness, and headache in the standard care group and headache in the ferric carboxymaltose group.

Secondary Endpoint(s):

- Efficacy in the multiple-dose study, as defined by the proportion of patients with a clinically meaningful increase in hemoglobin at any time between baseline and the end of study or time of intervention: 64% with ferric carboxymaltose, 57% with iron sucrose or sodium ferric gluconate complex, 45% with oral iron, and 52% with other treatments.

Limitations: Comparator treatment was selected at investigator discretion and was not standardized.

Drug: Ferric Carboxymaltose vs Iron Sucrose

Reference: Christoph P, et al, 2012²⁰

Study Design: Retrospective analysis from 2 Swiss hospitals

Study Funding: Vifor Pharma

Patients: 206 pregnant women treated with ferric carboxymaltose (103 patients after February 2008) or iron sucrose (103 patients from 2005 through 2007) for iron deficiency anemia and intolerance of oral iron, insufficient hemoglobin response after oral iron, or need for rapid hemoglobin increase.

Intervention: Ferric carboxymaltose up to 1,300 mg/wk (mean dose, 13 mg/kg/wk or 933 mg per

patient per week [13 patients received more than 1 dose]), or iron sucrose 400 mg/wk in 2 infusions 48 hours apart and repeated as needed (mean dose, 6 mg/kg/wk or 402 mg per patient per week [47 patients received more than 1 dose]).

Results:

Primary Endpoint(s):

- Maternal adverse effects: no significant difference.

Secondary Endpoint(s):

- Efficacy in women with ferritin levels of 30 mcg/L or less at baseline: Hemoglobin increased 1.54 g/dL with ferric carboxymaltose and 1.17 g/dL with iron sucrose ($P = .0819$).
- Fetal safety: No signs of negative effects on the fetus were detected.

Comments: For most patients, the total dose of ferric carboxymaltose was 1,000 mg IV; the total iron sucrose dose was not reported.

Limitations: This was a retrospective study. Groups were not treated during the same period of time.

Reference: Pfenniger A, et al, 2012²¹

Study Design: Retrospective cohort study

Study Funding: Not specified

Patients: 210 postpartum women with iron deficiency anemia requiring IV iron treatment due to intolerance of oral iron, insufficient hemoglobin response after oral iron, or need for rapid hemoglobin increase.

Intervention: Ferric carboxymaltose 15 mg/kg (maximum, 100 mg; 105 women treated from 2008 through 2010), or iron sucrose 200 mg repeated once within 48 hours (105 women treated from 2005 through 2008).

Results:

Primary Endpoint(s):

- Adverse effects: no significant difference.

Secondary Endpoint(s):

- Hemoglobin change from baseline: 1.29 g/dL with ferric carboxymaltose and 0.93 g/dL with iron sucrose ($P = .26$).

Limitations: This was a retrospective study. Groups were not treated during the same period of time, and doses were not comparable. Follow-up was only for 8 days.

Reference: Evstatiev R, et al, 2011²²

Study Design: Randomized, open-label, multicenter study

Study Funding: Vifor Pharma

Patients: 485 patients with iron deficiency anemia and mild to moderate inflammatory bowel disease, hemoglobin of 7 to 12 g/dL in females and 7 to 13 g/dL in males, and ferritin less than 100 ng/mL.

Intervention: Ferric carboxymaltose up to 1,000 mg IV over 15 minutes weekly for up to 3 infusions, or iron sucrose 200 mg IV over 30 minutes twice weekly for up to 11 infusions. The mean iron dose was 1,377 mg in the ferric carboxymaltose group and 1,160 mg in the iron sucrose group.

Results:

Primary Endpoint(s):

- Increase in hemoglobin of at least 2 g/dL at week 12: 65.8% of patients treated with ferric carboxymaltose and 53.6% treated with iron sucrose ($P = .004$).

Secondary Endpoint(s):

- Normal hemoglobin (12 g/dL or greater in females and 13 g/dL or greater in males): 72.8% of patients in the ferric carboxymaltose group and 61.8% in the iron sucrose group ($P = .015$).
- Normal transferrin saturation (20% to 50%): 52.7% with ferric carboxymaltose and 36.4% with iron sucrose ($P < .001$).
- Normal ferritin (100 ng/mL or greater): 42.5% with ferric carboxymaltose and 27.3% with iron sucrose ($P = .001$).
- Normal hemoglobin plus normal ferritin: 31.1% in the ferric carboxymaltose group and 16.7% in the iron sucrose group ($P < .001$).
- Quality of life: Scores improved by week 12 with both agents.
- Treatment-related adverse events: 13.9% with ferric carboxymaltose and 11.3% with iron sucrose ($P = .413$).

Comments: The mean number of infusions was 2.1 in the ferric carboxymaltose group and 5.8 in the iron sucrose group ($P < .001$). Full adherence to the regimen was achieved in 92.5% of patients in the ferric carboxymaltose group compared with 79.1% of patients in the iron sucrose group ($P < .001$).

Drug: Ferric Carboxymaltose vs Ferrous Sulfate

Reference: Van Wyck DB, et al, 2009²³

Study Design: Randomized, open-label, multicenter study

Study Funding: American Regent Division of Luitpold Pharmaceuticals

Patients: 477 women with iron deficiency anemia (hemoglobin level less than 11 g/dL) secondary to heavy uterine bleeding.

Intervention: Ferric carboxymaltose up to 1,000 mg IV over 15 minutes weekly to achieve a total calculated replacement dose, or ferrous sulfate 325 mg (65 mg elemental iron) orally 3 times daily for 6 weeks.

Results:

Primary Endpoint(s):

- Hemoglobin increase of at least 2 g/dL: 82% of patients treated with ferric carboxymaltose and 61.8% treated with ferrous sulfate (95% CI for treatment difference, 12.2 to 28.3; $P < .001$).

Secondary Endpoint(s):

- Change in hemoglobin from baseline: Increase was greater with ferric carboxymaltose than with ferrous sulfate on days 14, 28, and 42 ($P < .001$).
- Hemoglobin increase of at least 3 g/dL: 53% of patients treated with ferric carboxymaltose compared with 36% of patients treated with ferrous sulfate ($P < .001$).
- Hemoglobin level of at least 12 g/dL: 72.8% of patients treated with ferric carboxymaltose compared with 49.8% of patients treated with ferrous sulfate ($P < .001$).
- Serum ferritin levels were rapidly increased in the ferric carboxymaltose group but only increased slightly in the ferrous sulfate group ($P < .001$ at days 7, 14, 28, and 42).
- Quality of life: Patients treated with ferric carboxymaltose reported greater improvement in vitality, physical function, and symptoms of fatigue in quality-of-life assessments ($P < .05$).

Other Endpoint(s):

- Patients treated with oral iron experienced more constipation, diarrhea, nausea, and vomiting, while those treated with ferric carboxymaltose experienced more fatigue, headache, dizziness, dysgeusia, and rash.

Reference: Seid MH, et al, 2008²⁴

Study Design: Randomized, open-label, multicenter study

Study Funding: American Regent

Patients: 291 women with postpartum iron deficiency anemia (hemoglobin levels 10 g/dL or less within 10 days of delivery).

Intervention: Ferric carboxymaltose 1,000 mg or less IV over 15 minutes or less and repeated weekly to a calculated iron replacement dose (maximum, 2,500 mg), or ferrous sulfate 325 mg orally 3 times daily for 6 weeks. Mean iron exposure was 1,503.5 mg in the ferric carboxymaltose group and 7,906.1 mg in the oral iron group.

Results:**Primary Endpoint(s):**

- Hemoglobin levels of 12 g/dL or greater: 91.4% of patients in the ferric carboxymaltose group compared with 66.7% of patients in the ferrous sulfate group ($P < .001$).

Secondary Endpoint(s):

- Hemoglobin increase of 3 g/dL or greater: 91.4% of patients in the ferric carboxymaltose group compared with 64.6% in the ferrous sulfate group ($P < .0001$).
- Median time to achieve a hemoglobin level greater than 12 g/dL: 14 days in the ferric carboxymaltose group compared with 27 days in the ferrous sulfate group ($P = .0002$).
- Median time to achieve a hemoglobin increase of 3 g/dL or greater: 15 days in the ferric carboxymaltose group compared with 28 days in the ferrous sulfate group ($P < .0001$).
- Change in ferritin from baseline: increased with ferric carboxymaltose but not with ferrous sulfate ($P < .0001$).
- Change in transferrin saturation from baseline: increased to a greater extent with ferric carboxymaltose at each time point compared with ferrous sulfate ($P < .0001$).
- Sustained increase in hemoglobin levels to at least 12 g/dL at day 42: 85.4% of patients in the ferric carboxymaltose group compared with 58% of patients in the ferrous sulfate group ($P < .0001$).

Other Endpoint(s):

- Adverse events occurring more frequently in the ferric carboxymaltose group included urticaria and dysgeusia; those occurring more frequently with oral iron included constipation, abdominal pain, and elevated liver enzymes.

Reference: Van Wyck DB, et al, 2007²⁵

Study Design: Randomized, open-label, multicenter, noninferiority study

Study Funding: American Regent Division of Luitpold Pharmaceuticals

Patients: 352 women with postpartum iron deficiency anemia (hemoglobin levels less than 10 g/dL within 10 days postpartum).

Intervention: Ferric carboxymaltose 15 mg/kg (up to 1,000 mg) IV over 15 minutes repeated weekly to a total calculated replacement dose (174 patients; maximal total dose of 2,500 mg), or oral ferrous sulfate 325 mg 3 times daily for 6 weeks (178 patients). The mean total ferric carboxymaltose

dose was 1,403.1 mg; the majority of patients (79.3%) required 2 doses.

Results:**Primary Endpoint(s):**

- Hemoglobin increase of 2 g/dL or greater: 96.4% of patients treated with ferric carboxymaltose and 94.1% treated with ferrous sulfate ($P = .443$; met noninferiority criteria).

Secondary Endpoint(s):

- Time to achieve hemoglobin increase of 2 g/dL or greater: mean of 7 days with ferric carboxymaltose and 14 days with ferrous sulfate ($P < .001$).
- Hemoglobin increase of 3 g/dL or greater: 86.3% of patients treated with ferric carboxymaltose compared with 60.4% treated with ferrous sulfate ($P < .001$).
- Hemoglobin increased to greater than 12 g/dL: 90.5% of patients treated with ferric carboxymaltose and 68.6% treated with ferrous sulfate ($P < .001$).
- Maximal increase in ferritin, transferrin saturation, reticulocyte count, or reticulocyte hemoglobin content: Serum ferritin levels increased in the IV group, but not in the oral group; transferrin saturation was increased in both groups.
- Quality of life: Similar improvements in quality-of-life assessment scores were observed in the 2 treatment groups.

Reference: Breymann C, et al, 2008²⁶

Study Design: Randomized, open-label, multicenter, noninferiority study

Study Funding: Vifor Pharma

Patients: 349 women with postpartum iron deficiency anemia (hemoglobin levels less than 10.5 g/dL).

Intervention: Ferric carboxymaltose 15 mg/kg (up to 1,000 mg) IV administered over 15 minutes weekly for up to 3 weeks, or ferrous sulfate 100 mg orally twice daily for 12 weeks; mean total ferric carboxymaltose dose was 1,346.7 mg.

Results:**Primary Endpoint(s):**

- Hemoglobin change from baseline to week 12: 3.37 g/dL in the ferric carboxymaltose group and 3.29 g/dL in the ferrous sulfate group (met noninferiority endpoint).

Secondary Endpoint(s):

- Change in ferritin from baseline to week 12: increased from 39.9 to 161.2 ng/mL with ferric carboxymaltose and from 32.4 to 43.3 ng/mL with ferrous sulfate ($P < .001$).

- Change in transferrin saturation from baseline to week 12: greater with ferric carboxymaltose ($P < .001$); specific values not reported.
- Response (hemoglobin level of 12 to 16 g/dL): 84.9% with ferric carboxymaltose and 82% with ferrous sulfate.
- Response (ferritin level of 50 to 800 ng/mL): 77.7% with ferric carboxymaltose and 32.6% with ferrous sulfate ($P < .001$).
- Response (transferrin saturation of 20% to 50%): 77.7% with ferric carboxymaltose and 66.3% with ferrous sulfate ($P < .05$).
- Transfusions: required in 1 patient in the ferric carboxymaltose group and no patients in the ferrous sulfate group.

Reference: Kulnigg S, et al, 2008²⁷

Study Design: Randomized, open-label, multicenter, noninferiority study

Study Funding: Vifor Pharma

Patients: 200 patients with anemia secondary to inflammatory bowel disease, with hemoglobin of 11 g/dL or less and transferrin saturation less than 20%, or serum ferritin less than 100 ng/mL.

Intervention: Ferric carboxymaltose up to 1,000 mg IV weekly until the total calculated iron dose was reached (137 patients), or ferrous sulfate 100 mg orally twice daily for 12 weeks (63 patients).

Results:

Primary Endpoint(s):

- Change in hemoglobin from baseline to week 12: improved from 8.7 to 12.3 g/dL in the ferric carboxymaltose group and from 9.1 to 12.1 g/dL in the ferrous sulfate group; these differences were within the noninferiority limits ($P = .7$).

Secondary Endpoint(s):

- Change in serum ferritin from baseline to week 2, 4, 8, and 12: increased from 5 to 43.5 ng/mL with ferric carboxymaltose and from 6.5 to 28.5 ng/mL with ferrous sulfate at week 12.
- Change in transferrin saturation from baseline to weeks 2, 4, 8, and 12: increased from 4% to 23% at week 2 and decreased to 17.5% at week 12 with ferric carboxymaltose, and from 6% to 17% at week 2 and to 22% at week 12 with ferrous sulfate.
- Patients achieving target levels of hemoglobin (13.5 to 18 g/dL for men and 12 to 16 g/dL for women): Results were not reported.
- Patients with an increase in hemoglobin levels of at least 2 g/dL: greater in the ferric carboxymal-

tose group at weeks 2 ($P = .0051$) and 4 ($P = .03$), but similar at weeks 8 and 12 (76.5% with ferric carboxymaltose and 68.3% with ferrous sulfate at week 12).

- Patients achieving target levels of ferritin (100 to 800 ng/mL): greater in the ferric carboxymaltose group at all time points ($P < .001$; 26.5% with ferric carboxymaltose vs 3.3% with ferrous sulfate at week 12).
- Patients achieving target levels of transferrin saturation (20% to 50%): greater in the ferric carboxymaltose group at week 2 ($P < .001$) and week 4 ($P = .013$), but similar at week 12.
- Patients discontinuing due to lack of response: none in either group.

Other Endpoint(s):

- Treatment-related adverse events: 28.5% of patients in the ferric carboxymaltose group and 22.2% in the ferrous sulfate group.

Reference: Bisbe E, et al, 2011²⁸

Study Design: Prospective cohort study, with historical control

Study Funding: Vifor-Uriach, Barcelona, Spain (ferric carboxymaltose donated by manufacturer)

Patients: 76 surgical patients with preoperative anemia prospectively treated with ferric carboxymaltose were compared with 84 surgical patients with preoperative anemia historically treated with iron sucrose.

Intervention: Ferric carboxymaltose 500 to 1,000 mg per session or iron sucrose 100 to 200 mg per session to replenish total iron deficiency; mean total IV iron dose was 1,120 mg with ferric carboxymaltose and 1,010 mg with iron sucrose.

Results:

Primary Endpoint(s):

- Mean change in hemoglobin from baseline to last assessment before surgery: 2.1 g/dL with ferric carboxymaltose and 2 g/dL with iron sucrose. Hemoglobin levels increased from 10.1 g/dL at baseline to 12.1 g/dL at the last assessment before surgery in the iron sucrose group, and from 10.4 g/dL at baseline to 12.5 g/dL at the last assessment before surgery in the ferric carboxymaltose group ($P < .05$).

Secondary Endpoint(s):

- Number of IV iron administration sessions: 2 with ferric carboxymaltose and 5 with iron sucrose ($P < .001$).
- Response (hemoglobin increase of at least 1.5 g/dL or final hemoglobin of 13 g/dL or greater):

70% with ferric carboxymaltose and 67% with iron sucrose.

- Anemic correction (defined as an increase in hemoglobin levels to at least 12 g/dL in women and 13 g/dL in men): 59% of patients treated with iron sucrose and 72% of patients treated with ferric carboxymaltose.

Comments: Despite comparable iron deficit at baseline (950 mg in the ferric carboxymaltose group and 1,000 mg in the iron sucrose group), the ferric carboxymaltose–treated patients received a higher mean total iron dose.

Limitations: The comparator group was a historical control.

Drug: Ferric Carboxymaltose, Iron Dextrose, Iron Sucrose

Reference: Dillon R, et al, 2012²⁹

Study Design: Retrospective, single-center review of medical records

Study Funding: None specified

Patients: 208 adult patients with iron deficiency anemia treated with IV iron over a 2-year period in a single center; patients with CKD were excluded.

Intervention: 82 patients received ferric carboxymaltose 500 mg slow IV bolus (body weight less than 60 kg) or a 1 g IV infusion over 30 minutes (body weight greater than 60 kg); 42 patients received iron dextran 20 mg/kg IV infusion; 84 patients received iron sucrose 200 mg IV infusion over 2 hours, repeated a variable number of times within 7 to 14 days (median, 4 infusions; range, 3 to 6 infusions).

Results:

Primary Endpoint(s):

- Mean change in hemoglobin 6 weeks after the infusion (or last infusion in the iron sucrose group): 2.7 g/dL with ferric carboxymaltose ($P < .01$ vs iron dextran), 1.4 g/dL with iron dextran, and 2.4 g/dL with iron sucrose ($P = .004$ vs iron dextran).

Secondary Endpoint(s):

- Mean change in serum ferritin: 149 mcg/dL with ferric carboxymaltose, 149 mcg/dL with iron dextran, and 109 mcg/dL with iron sucrose.
- Mean change in mean corpuscular volume: 7 fL with ferric carboxymaltose, 5.8 fL with iron dextrose, and 5.6 fL with iron sucrose.

Limitations: This was a retrospective analysis of medical records from a single center.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS:

Contraindications

Ferric carboxymaltose is contraindicated in patients with known hypersensitivity to ferric carboxymaltose or any of the product excipients.¹

The contraindications, warnings, and precautions of the available parenteral iron products are compared in Table 3.

Warnings and Precautions

Parenteral iron formulations, including ferric carboxymaltose, can cause hypersensitivity reactions, including potentially fatal anaphylactoid reactions. Facilities for cardiopulmonary resuscitation must be available during ferric carboxymaltose administration. Patients should be monitored for signs and symptoms of hypersensitivity during and for at least 30 minutes after administration and until clinically stable. In clinical trials, serious anaphylactic/anaphylactoid reactions were reported in 0.1% (2 of 1,775) of patients receiving ferric carboxymaltose. Other serious reactions potentially related to hypersensitivity, including pruritus, rash, urticaria, wheezing, or hypotension, occurred in 1.5% (26 of 1,775) of patients.¹

Hypertension was reported in 3.8% (67 of 1,775) of patients treated with ferric carboxymaltose in clinical trials, while transient elevations in systolic blood pressure sometimes accompanied by facial flushing, dizziness, or nausea occurred in 6% (106 of 1,775) of patients. These elevations generally occurred immediately after dosing and resolved within 30 minutes. Patients should be monitored for hypertension following administration of each ferric carboxymaltose dose.¹

Laboratory assays may overestimate serum iron and transferrin-bound iron in the 24 hours following ferric carboxymaltose administration by also measuring the iron in the product.¹

Caution is necessary to avoid extravasation when administering ferric carboxymaltose. Leakage could result in brown discoloration and irritation of the skin. In the case of extravasation, ferric carboxymaltose administration should be immediately stopped.¹

Safety and effectiveness have not been established in pediatric patients.¹

Ferric carboxymaltose is assigned Pregnancy Category C. Fetal malformations and increased implantation losses were observed in animal studies at maternally toxic doses. Studies in pregnant women have not been

Table 3. Contraindications, warnings, and precautions for parenteral iron products^{1,30-34}

	Ferric carboxymaltose	Ferumoxytol	Iron dextran	Iron sucrose	Sodium ferric gluconate complex
<i>Contraindication</i>					
Hypersensitivity	X	X	X	X	X
<i>Black box warning</i>					
Risk of anaphylactic-type reactions			X		
<i>Warnings and precautions</i>					
Hypersensitivity reactions	X	X	X	X	X
Hypertension	X				
Hypotension		X		X	X
Iron overload		X	X	X	X
Laboratory test alterations	X				
MRI diagnostic ability affected		X			
Delayed reactions			X		
Liver impairment			X		
Cardiovascular disease			X		
Acute infectious kidney disease			X		
Carcinogenesis with IM injections			X		
Benzyl alcohol toxicity					X
<i>Special populations</i>					
Elderly	No unique precautions	No unique precautions; dose cautiously	No unique precautions	No unique precautions; dose cautiously	No unique precautions; dose cautiously
Pediatric use	Not established	Not established	Not recommended in infants younger than 4 months	Iron maintenance treatment in patients 2 years and older; not established for iron replacement treatment or for use in patients younger than 2 years	Not established in children younger than 6 years. Contains benzyl alcohol; avoid use in neonates
Pregnancy	Category C	Category C	Category C	Category B	Category B
Breast-feeding	Use caution	Avoid use	Use caution	Use caution	Use caution

Note: IM = intramuscular.

conducted. Ferric carboxymaltose should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.¹

In 25 lactating women with postpartum iron deficiency, mean breast milk iron levels were higher in lactating women treated with ferric carboxymaltose than in lactating women receiving oral ferrous sulfate.¹

ADVERSE REACTIONS

Common adverse events include nausea, hypertension, flushing, dizziness, vomiting, injection-site discoloration, headache, dysgeusia, hypotension, constipation, abdominal pain, diarrhea, injection-site pain/irritation, rash, paresthesia, sneezing, increased gamma-glutamyl transferase, increased ALT, and blood phosphorus level reduction.¹

Table 4 shows adverse reactions reported in clinical trials when comparing ferric carboxymaltose with oral and IV iron products.

Administration of ferric carboxymaltose 15 mg/kg (maximum, 1,000 mg) over 15 minutes as an IV infusion was not associated with an increased incidence of severe adverse events compared with placebo in a crossover study that included 559 patients with iron deficiency anemia. Rates of nausea, headache, and dizziness were slightly increased.⁷

DRUG INTERACTIONS

Drug interactions specific to ferric carboxymaltose have not been identified.^{1,5}

RECOMMENDED MONITORING

Hemoglobin levels and iron status should be monitored periodically throughout therapy.¹

Patients should be monitored for extravasation during administration. If extravasation occurs, administration at that site should be discontinued.¹

DOSING

For patients weighing 50 kg or more, ferric carboxymaltose is recommended in two 750 mg doses separated by at least 7 days, for a total cumulative dose not exceeding 1,500 mg of iron per course. For patients weighing less than 50 kg, ferric carboxymaltose is recommended in two 15 mg/kg doses separated by at least 7 days, for a total cumulative dose not exceeding 1,500 mg of iron per course. Treatment may be repeated if iron deficiency anemia recurs.¹

Ferric carboxymaltose is administered IV as an undiluted slow IV push at a rate of approximately 100 mg (2 mL) per minute or as an IV infusion diluted in no more than 250 mL of sterile sodium chloride 0.9% injection administered over at least 15 minutes.¹ In clinical trials, ferric carboxymaltose has been administered as 100 or 200 mg undiluted injections over 1 to 2 minutes, and at dosages of up to 1,000 mg as short infusions (10 to 30 minutes) in 100 to 250 mL of sodium chloride 0.9% solution.^{2-4,15,25,27,28} European labeling includes an IV bolus dosage of up to 200 mg/day no more than 3 times a week and an IV infusion dosage of up to 1,000 mg (not to exceed 15 mg/kg) no more than once a week.⁵

Table 4. Iron product–related adverse reactions ($\geq 1\%$ of study patients)¹

	Ferric carboxymaltose (<i>n</i> = 1,775)	Oral or IV iron comparator (<i>n</i> = 1,783)	Oral iron (<i>n</i> = 253)
Nausea	7.2%	1.8%	1.2%
Hypertension	3.8%	1.9%	0.4%
Flushing/hot flush	3.6%	0.2%	0%
Blood phosphorus decrease	2.1%	0.1%	0%
Dizziness	2%	1.2%	0%
Vomiting	1.7%	0.5%	0.4%
Injection-site discoloration	1.4%	0.3%	0%
Headache	1.2%	0.9%	0%
ALT increase	1.1%	0.2%	0%
Dysgeusia	1.1%	2.1%	0%
Hypotension	1%	1.9%	0%
Constipation	0.5%	0.9%	3.2%

Note: ALT = alanine aminotransferase; IV = intravenous.

Table 5. Dosing and administration for parenteral iron products^{1,5,30-34,36}

	Ferric carboxymaltose (<i>Injectafer</i>)	Ferumoxytol	Iron dextran (<i>Dexferrum</i>)	Iron dextran (<i>INFeD</i>)	Iron sucrose	Sodium ferric gluconate complex
Test dose	No	No	Test dose of 0.5 mL IV over ≥ 5 min required; 1 hour should elapse prior to administration of the remainder of the initial dose	Test dose of 0.5 mL IV over ≥ 30 seconds or 0.5 mL IM required; 1 hour should elapse prior to administration of the remainder of the initial IV dose	No	No
Adult dose (IV)	Body weight ≥ 50 kg: Two 750 mg doses separated by ≥ 7 days	Initial 510 mg IV dose, followed by a second 510 mg IV dose 3 to 8 days later	≤ 2 mL (100 mg) daily until the calculated total iron amount is reached	≤ 2 mL (100 mg) daily until the calculated total iron amount is reached	Hemodialysis patients: 100 mg per consecutive hemodialysis session until usual 1,000 mg treatment dose is achieved	10 mL (125 mg) IV per consecutive hemodialysis session until usual 1,000 mg treatment dose is achieved
	Body weight < 50 kg: Two 15 mg/kg doses separated by ≥ 7 days				CKD patients not on dialysis: 200 mg as a slow IV injection on 5 occasions over a 14-day period, or 500 mg IV over 3.5 to 4 hours on days 1 and 14	
					CKD patients receiving peritoneal dialysis: 300 mg IV over 1.5 hours on days 1 and 14, then 400 mg IV over 2.5 hours on day 28	
Maximum single approved IV dose	750 mg (not to exceed 15 mg/kg)	510 mg	100 mg	100 mg	500 mg	125 mg

(continued)

Table 5. Dosing and administration for parenteral iron products^{1,5,30-34,36} (CONT.)

	Ferric carboxymaltose (<i>Injectafer</i>)	Ferumoxitol	Iron dextran (<i>Dexferrum</i>)	Iron dextran (<i>INFeD</i>)	Iron sucrose	Sodium ferric gluconate complex
IV rate	Undiluted as slow IV push at a rate of approximately 100 mg (2 mL) per minute or diluted in up to 250 mL as infusion over ≥ 15 minutes	1 mL/s (30 mg/s)	Not to exceed 1 mL/min (50 mg/min)	Not to exceed 1 mL/min (50 mg/min)	Undiluted as slow IV injection over 2 to 5 min; 100 mg diluted in up to 100 mL as infusion over ≥ 15 minutes; 500 mg diluted in up to 250 mL as infusion over 3.5 to 4 hours; 300 mg diluted in up to 250 mL as infusion over 1.5 hours; 400 mg diluted in up to 250 mL as infusion over 2.5 hours	Undiluted as slow IV injection at a rate of up to 12.5 mg/min; diluted in 100 mL as infusion over 1 hour
Dilution	Undiluted or diluted in up to 250 mL of sodium chloride 0.9%	Undiluted	Undiluted	Undiluted	Undiluted or diluted as 100 mg in up to 100 mL of sodium chloride 0.9%, or 300 to 500 mg in up to 250 mL of sodium chloride 0.9%; do not dilute to <1 mg/mL	Undiluted or diluted as 125 mg in 100 mL of sodium chloride 0.9%, or pediatric 0.12 mL/kg dose in 25 mL of sodium chloride 0.9%
Total dose infusion possible ^a	No	No	Yes	Yes	No	No
Adult dose (IM)	—	—	—	≤ 2 mL (100 mg) daily until the calculated total iron amount is reached; administer IM deeply into the upper outer quadrant of the buttock using the Z-track technique	—	—

(continued)

Table 5. Dosing and administration for parenteral iron products^{1,5,30-34,36} (CONT.)

	Ferric carboxymaltose (<i>Injectafer</i>)	Ferumoxytol	Iron dextran (<i>Dexferrum</i>)	Iron dextran (<i>INFeD</i>)	Iron sucrose	Sodium ferric gluconate complex
<i>Special populations</i>						
Pediatric	—	—	Do not exceed 0.5 mL (25 mg of iron) per day for infants <5 kg, 1 mL (50 mg of iron) per day for children <10 kg, or 2 mL (100 mg of iron) per day for other patients	Do not exceed 0.5 mL (25 mg of iron) per day for infants < 5 kg, 1 mL (50 mg of iron) per day for children <10 kg, or 2 mL (100 mg of iron) per day for other patients	Hemodialysis patients, iron maintenance treatment: 0.5 mg/kg, not to exceed 100 mg, every 2 weeks for 12 weeks; may be repeated if necessary CKD patients not on dialysis, iron maintenance treatment in patients on erythropoietin therapy: 0.5 mg/kg, not to exceed 100 mg, every 4 weeks for 12 weeks; may be repeated if necessary CKD patients receiving peritoneal dialysis, iron maintenance treatment in patients on erythropoietin therapy: 0.5 mg/kg, not to exceed 100 mg, every 4 weeks for 12 weeks; may be repeated if necessary	0.12 mL/kg (1.5 mg/kg) at 8 consecutive dialysis sessions, not to exceed 125 mg per dose
Elderly	No dosage adjustment required	No dosage adjustment required	No dosage adjustment required	No dosage adjustment required	No dosage adjustment required	No dosage adjustment required
Renal impairment	No dosage adjustment required	No dosage adjustment required	No dosage adjustment required	No dosage adjustment required	No dosage adjustment required	No dosage adjustment required
Hepatic impairment	No dosage adjustment required	No dosage adjustment required	No dosage adjustment required	No dosage adjustment required	No dosage adjustment required	No dosage adjustment required

Note: CKD = chronic kidney disease; IM = intramuscular; IV = intravenous.

^aNot FDA approved.

Table 6. Agents in the parenteral iron class^{1,30-34}

	Ferric carboxymaltose	Ferumoxytol	Iron dextran	Iron sucrose	Sodium ferric gluconate complex
Brand name	<i>Injectafer</i>	<i>Feraheme</i>	<i>Dexferrum</i> <i>INFeD</i>	<i>Venofer</i>	<i>Ferrlecit</i>
Manufacturer	American Regent	AMAG	American Regent, Watson	American Regent, Fresenius	sanofi-aventis
Dosage forms and strengths available	IV solution: 750 mg per 15 mL	IV solution: 510 mg per 17 mL	Injection solution: 50 mg/mL	IV solution: 20 mg/mL in 2.5, 5, and 10 mL vials	IV solution: 12.5 mg/mL in 5 mL ampules or vials
Elemental iron content	50 mg/mL	30 mg/mL	50 mg/mL	20 mg/mL	12.5 mg/mL
Generic availability	No	No	No	No	Yes

Note: IV = intravenous.

Table 5 compares the dosing and administration for the parental iron products.

PRODUCT AVAILABILITY

Ferric carboxymaltose injection received FDA approval on July 25, 2013. It is available as an IV solution in single-use vials containing 750 mg of iron per 15 mL, supplied individually boxed and in packages of 2 vials.¹ It should be stored at 20°C to 25°C (68°F to 77°F), with excursions permitted to 15°F to 30°C (59°F to 80°F). The product should not be frozen.¹

Table 6 compares the dosage forms and strengths available for the parenteral iron products.

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

No REMS is required for ferric carboxymaltose or any other parenteral iron product.

CONCLUSION

Ferric carboxymaltose is effective for iron replacement in patients with iron deficiency anemia. Ferric carboxymaltose has efficacy comparable with or greater than IV iron sucrose and oral iron in patients with iron deficiency anemia associated with CKD, gynecologic bleeding, inflammatory bowel disease, and other medical conditions. It appears to be very well tolerated, permitting administration of dosages of up to 750 mg weekly, which results in rapid replacement of iron stores and a quick therapeutic response.

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Continuing Education Case Study Quiz

Goal—The goal of this program is to educate pharmacists about the use of ferric carboxymaltose for the treatment of patients with iron deficiency anemia.

Objectives—At the completion of this program, the reader will be able to:

1. Describe the pharmacology and pharmacokinetics of ferric carboxymaltose.
2. Discuss the risks associated with the use of ferric carboxymaltose.
3. Discuss the dosage, reconstitution, and administration of ferric carboxymaltose.
4. Apply the information on the use of ferric carboxymaltose.

Key Words—anemia, ferric carboxymaltose, new drugs, parenteral iron

1. A US Food and Drug Administration (FDA)–approved indication for ferric carboxymaltose is:
 - a. As a supplement to oral iron in patients with iron deficiency.
 - b. Treatment of iron deficiency anemia in adults with nondialysis-dependent chronic kidney disease (CKD).
 - c. Treatment of postpartum iron deficiency anemia.
 - d. Treatment of iron deficiency anemia in patients with hemodialysis-dependent CKD.
2. Ferric carboxymaltose is best described as:
 - a. A coated magnetite complex.
 - b. An iron-carbohydrate complex.
 - c. An iron dextran complex.
 - d. An iron sucrose complex.
3. Following intravenous (IV) administration, ferric carboxymaltose is rapidly distributed to which organs?
 - a. Bone marrow, kidneys, and liver
 - b. Bone marrow, liver, and spleen
 - c. Duodenum, kidneys, and liver
 - d. Liver, lungs, and spleen
4. Ferric carboxymaltose has a terminal elimination half-life of:
 - a. 1 hour
 - b. 6 hours
 - c. 7 to 12 hours
 - d. 9 to 87 hours
5. In the study by Qunibi et al comparing ferric carboxymaltose with oral iron in nondialysis-dependent CKD patients, what proportion of patients receiving ferric carboxymaltose had a hemoglobin increase of at least 1 g/dL?
 - a. 34.7%
 - b. 26.2%
 - c. 60.4%
 - d. 28.6%
6. Which adverse reaction was observed at a rate at least 5% greater in patients treated with ferric carboxymaltose than oral or IV iron comparators?
 - a. Constipation
 - b. Hypertension
 - c. Nausea
 - d. Vomiting
7. Which of the following is the maximum recommended dose of ferric carboxymaltose?
 - a. 15 mg/kg, 2 doses separated by at least 7 days for up to 1,000 mg/course
 - b. 750 mg/day, 2 doses separated by at least 7 days for up to 1,500 mg/course
 - c. 15 mg/kg, 3 doses separated by at least 7 days for up to 1,500 mg/course
 - d. 1,500 mg/day, 2 doses separated by at least 7 days for up to 1,500 mg/course
8. The maximum recommended rate of IV administration of ferric carboxymaltose is:
 - a. 12.5 mg/min.
 - b. 50 mg/min.
 - c. 100 mg/min.
 - d. 30 mg/s.

Case Study

A.R. is a 62-year-old female, weighing 105.6 lbs, with a history of hypertriglyceridemia and iron deficiency anemia secondary to inflammatory bowel disease. She is currently taking alendronate 70 mg once weekly, mesalamine 800 mg 3 times daily for 6 week cycles, ferrous sulfate 100 mg twice daily, and niacin 500 mg 3 times daily. Her doctor would like to switch her to ferric carboxymaltose due to insufficient response to oral ferrous sulfate.

9. What is an appropriate maximum weekly dose of ferric carboxymaltose for A.R.?
 - a. Daily administration of 100 mg IV until the calculated total iron amount has been reached.
 - b. Two 720 mg doses separated by at least 7 days.
 - c. Two 750 mg doses separated by at least 7 days.
 - d. Two 1,440 mg doses separated by at least 7 days.
10. Following preparation of the IV dose for A.R., some ferric carboxymaltose solution remains in the vial. What should be done with any quantity remaining in the vial?
 - a. Immediately discard.
 - b. Store in the freezer for preparation of another dose.
 - c. Store in the refrigerator for preparation of another dose.
 - d. Store at room temperature for preparation of A.R.'s next dose.
11. Recommended monitoring for A.R. during and for 30 minutes after the ferric carboxymaltose infusion includes:
 - a. Blood pressure.
 - b. Hemoglobin levels and iron status.
 - c. Signs and symptoms of hypersensitivity.
 - d. a and c
12. Additional recommended monitoring for patients treated with ferric carboxymaltose includes:
 - a. Blood glucose and hemoglobin levels.
 - b. Hemoglobin levels and bilirubin.
 - c. Hemoglobin levels and iron status.
 - d. Serum creatinine, hepatic transaminases, and iron status.
13. During infusion of her second dose, A.R. reports a brown discoloration of her skin near the infusion site. What is your immediate course of action?
 - a. Reduce the infusion rate of ferric carboxymaltose by one-half.
 - b. Stop infusion of ferric carboxymaltose.
 - c. Change the site of administration of ferric carboxymaltose.
 - d. No action is required; finish the administration and rotate sites at the next weekly visit.
14. Guidelines for anemia in CKD advise avoidance IV iron products, including ferric carboxymaltose, in patients with:
 - a. Active systemic infections.
 - b. Hepatic dysfunction.
 - c. Iron deficiency anemia.
 - d. Renal dysfunction.
15. Following administration of ferric carboxymaltose, laboratory assays may overestimate serum iron and transferrin-bound iron for up to:
 - a. 12 hours.
 - b. 24 hours.
 - c. 72 hours.
 - d. 1 week.

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