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Total Cost of Care Reduction in IDA Patients With Ferric Carboxymaltose

INTRODUCTION

There are millions of adults in the United States with iron deficiency anemia (IDA), a condition in which patients have low hemoglobin (Hb) and insufficient iron.^{1,2} IDA can lead to decreased blood oxygen that results in a range of symptoms.³ Individuals with certain comorbid conditions, such as heart failure (HF), chronic kidney disease (CKD), and cancer are at increased risk of developing IDA, and those with IDA experience worse clinical outcomes and increased health care costs.⁴⁻⁸ Treatment of IDA aims to normalize Hb levels and increase iron stores in the body.³ Intravenous (IV) iron therapy is commonly recommended for many patients with IDA, and especially for those with certain chronic conditions (eg, HF, CKD, cancer).² There are several different IV iron formulations available, with some formulated to be administered at lower doses over the course of several visits, and newer formulations designed to be administered at higher doses over fewer visits.⁹ A retrospective claims analysis examined the differences in total cost of care among patients with IDA before and after treatment with different IV iron formulations, and also conducted subanalyses of cost differences in patients with IDA and HF, CKD, or cancer.¹⁰ Compared with patients who received low-dose iron (LDI) therapies, those who were treated with the high-dose formulation ferric carboxymaltose (FCM) injection (Injectafer; Daiichi Sankyo, Inc) had greater cost reductions from pre- to post-IV iron treatment.¹⁰ These findings suggest that FCM may be a more cost-effective option for patients requiring IV iron therapy, especially in populations with substantial comorbidities, making it a valuable option in the landscape of IDA treatment.¹⁰

IRON DEFICIENCY ANEMIA

Iron deficiency (ID), anemia, and IDA are 3 interconnected conditions.⁴ Anemia is defined as low blood Hb.³ In ID, depleted iron stores are due to an imbalance between iron uptake and iron utilization.^{2,11} Whereas ID can be present with or without anemia,^{4,11} continued iron loss can lead to development of IDA.²

IDA is a common type of anemia that occurs when iron levels are insufficient to generate healthy red blood cells.^{2,12} IDA is the leading cause of anemia worldwide.² Approximately 6,500,000 adults in the United States have IDA.¹

IMPORTANT SAFETY INFORMATION INDICATIONS

Injectafer® (ferric carboxymaltose injection) is indicated for the treatment of iron deficiency anemia (IDA) in adult and pediatric patients 1 year of age and older who have either intolerance or an unsatisfactory response to oral iron, and in adult patients who have non-dialysis dependent chronic kidney disease. Injectafer is also indicated for iron deficiency in adult patients with heart failure and New York Heart Association class II/III to improve exercise capacity.

CONTRAINDICATIONS

Injectafer is contraindicated in patients with hypersensitivity to Injectafer or any of its inactive components.

FOUNDER

Mike Hennessy Sr | 1960-2021

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Signs and Symptoms

The signs and symptoms of IDA can overlap with and exacerbate other chronic conditions and are often nonspecific, such as fatigue, dizziness, and shortness of breath.^{3,12} Additionally, some patients with IDA may be asymptomatic.² These considerations can complicate the diagnosis and management of IDA.³ Decreased blood oxygen levels consequent to low iron can eventually lead to reduced intestinal blood flow, resulting in malabsorption, nausea, weight loss, and abdominal pain.³ Furthermore, oxygen deficiency associated with IDA can lead to headaches, vertigo, lethargy, and eventually cognitive impairment.^{3,4}

Diagnosis of IDA includes measurement of Hb, ferritin, and transferrin saturation (TSAT).² These diagnostic criteria are interconnected since the production of Hb—the molecule that carries oxygen in red blood cells—requires sufficient levels of stored iron (ferritin) and available plasma iron (measured via TSAT).^{2,11,13} Patients who should be tested for IDA include those with certain chronic diseases such as HF, CKD, cancer, and other special populations with high rates of comorbid ID and IDA.^{4,14-16}

IDA WITH CHRONIC DISEASES

IDA is a common comorbidity in HF that can be both a cause and a sequela of HF.^{3,17} IDA can be associated with poor clinical status and worse prognosis in HF, and patients with HF and IDA have an increased mortality risk compared with individuals who have HF but no IDA.^{5,18} Approximately 17% of patients with chronic HF have IDA.¹⁸ In 2022, the American Heart Association (AHA), American College of Cardiology (ACC), and Heart Failure Society of America (HFSA) jointly released guidelines recommending routine baseline assessments (including complete blood count, ferritin, serum iron, and TSAT testing) be conducted in all patients with HF to evaluate for iron deficiency and anemia.¹⁴

IDA is also commonly seen in patients with nondialysis-dependent CKD (NDD-CKD).^{2,19} IDA is associated with an increased risk of

cardiovascular hospitalization and mortality among patients with NDD-CKD.⁶ While the prevalence of IDA in NDD-CKD is challenging to estimate and increases with stage of CKD, anemia is present in approximately 8% to 53% of patients with NDD-CKD,²⁰ and ID occurs in 15% to 48% of patients with NDD-CKD and anemia.¹⁹

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend screening for anemia in patients with CKD when clinically indicated, and further recommend assessing iron status in patients with anemia.¹⁵

Patients with cancer also frequently present with IDA.⁷ IDA can be associated with impaired physical function and performance status in those with cancer.^{7,21} Approximately 44% to 50% of patients with cancer (including hematologic malignancies) have IDA.⁷ National Comprehensive Cancer Network® (NCCN) Guidelines discuss the importance of evaluating for iron deficiency in patients with anemia and cancer, and also provide recommendations for IV iron treatment in appropriate patients.²² Guidelines from the European Society for Medical Oncology on management of chemotherapy-induced anemia in patients with solid or hematologic malignancies emphasize the importance of assessing Hb, iron status (TSAT, serum ferritin), and C-reactive protein prior to beginning chemotherapy treatment and before each treatment cycle.¹⁶

IDA also is common in certain patients with gastrointestinal (GI) conditions (ie, conditions that can cause decreased intestinal iron absorption, chronic blood loss, or inflammation), women with chronic blood loss or increased iron requirements (ie, those with abnormal uterine bleeding or who are pregnant, breastfeeding, or have recently given birth), and certain pediatric patients.^{4,13}

The Economic Impact of IDA in Chronic Diseases

Among patients with HF, CKD, and cancer, those with IDA experience considerably higher direct health care costs than do those without anemia.⁸ A retrospective cohort study of 1999–2001 MarketScan Commercial Claims and Encounters Database data estimated the

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IMPORTANT SAFETY INFORMATION (Continued) WARNINGS AND PRECAUTIONS

Symptomatic Hypophosphatemia

Symptomatic hypophosphatemia with serious outcomes including osteomalacia and fractures requiring clinical intervention has been reported in patients treated with Injestafer in the post-marketing setting. These cases have occurred mostly after repeated exposure to Injestafer in patients with no reported history of renal impairment. However, symptomatic hypophosphatemia has been reported after one dose. Possible risk factors for hypophosphatemia include a history of gastrointestinal disorders associated with malabsorption of fat-soluble vitamins or phosphate, inflammatory bowel disease, concurrent or prior use of medications that affect proximal renal tubular function, hyperparathyroidism, vitamin D deficiency, malnutrition, and hereditary hemorrhagic telangiectasia (HHT or Osler-Weber-Rendu syndrome). In most cases, hypophosphatemia resolved within three months.

differences in direct costs between more than 120,000 adults with comorbidities who had anemia (including IDA) and those who did not.⁸ After adjustment for factors including disease severity, age, sex, region, and insurance type, direct costs for those with IDA/anemia were \$30,452 greater for those with cancer, \$38,346 greater for those with CKD, and \$55,124 greater for those with congestive HF (note that costs have been inflated to 2024 US dollars).^{8,23} This analysis is limited by the use of administrative data that lack detailed clinical information such as severity of anemia; furthermore, the study sample may have been more likely to select for moderate-to-severe anemia, potentially leading to overestimation of the cost differences between patients with and without anemia.⁸

Studies specifically examining the economic impact in patients with HF show that those with anemia, ID, or IDA experience increased rates of hospitalization and readmission, longer mean length of stay, and higher health care costs.^{24,25}

An analysis from the Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits MarketScan[®] databases of 1999 data in 2760 patients with cancer receiving chemotherapy compared health care resource use and costs among those without anemia to those with anemia (n = 731) in the 3 months before or 6 months after initial cancer diagnosis.²⁶ Results showed significantly increased health care utilization for inpatient, outpatient, and outpatient prescription drug categories and significantly higher total 6-month medical expenditures among the anemic group (all, $P < .0001$).²⁶ While the analysis was limited by a lack of hemoglobin data that would have allowed for definitive determination of anemia status and severity, the authors emphasized that patients with anemia receiving chemotherapy use considerably more health care resources both inpatient and outpatient, even after controlling for possible confounders (including cancer type, metastasis, duration of chemotherapy, and cancer-related surgery or radiation therapy).²⁶

IDA TREATMENT

Recommended treatment options for patients with IDA vary based on the presence of an underlying or comorbid condition. However,

oral and IV iron therapy are 2 common treatment options.³ While oral iron supplementation often is an effective treatment for IDA, the long-term (3–6 months) treatment required to achieve iron repletion may be difficult to achieve due to associated GI adverse events (AEs) that can impact patient adherence and lead to treatment cessation.^{2,3}

Overall treatment goals are to replenish iron stores and normalize Hb levels.³ A retrospective analysis found that the mean iron deficit among patients with IDA of various etiologies was approximately 1500 mg.²⁷ This study calculated the average baseline iron deficit among 4641 patients treated with IV iron across 7 clinical studies.²⁷ In a separate post hoc analysis of data from a study in 2561 patients with NDD-CKD, those who received 1500 mg of iron were significantly less likely to require IV iron retreatment 2 to 3 months after initial treatment than were patients who received 1000 mg of iron (5.6% vs 11.1%, respectively; $P < .001$).²⁷ However, this analysis is limited by its retrospective design and authors note that various etiologies of IDA may respond differently to IV iron.²⁷

IV Iron Replacement Therapy in IDA

IV iron replacement therapies are indicated for many patients with IDA, including those with intolerance or an unsatisfactory response to oral iron supplementation, the need for quick recovery, and certain chronic conditions.² The 2022 AHA/ACC/HFSA guidelines recommend that patients with HF with reduced ejection fraction and ID/IDA be treated with an IV iron agent.¹⁴ The KDIGO guidelines also recommend IV iron treatment in appropriate patients with CKD and anemia or IDA.¹⁵

IV iron products are categorized as either first generation or second generation.⁹ First-generation IV iron products were formulated at lower doses that are administered over the course of several infusion visits, while newer second-generation products were formulated to be administered at higher doses with faster infusion times to more rapidly administer complete repletion doses.^{9,28–35}

First-generation IV iron products include iron dextran injection (ID) (INFeD; AbbVie), iron sucrose injection (IS) (Venofer; American Regent), and sodium ferric gluconate complex in sucrose injection (SFG) (Ferrlecit; Sanofi-Aventis).^{9,30–32}

IMPORTANT SAFETY INFORMATION (Continued) WARNINGS AND PRECAUTIONS (Continued)

Symptomatic Hypophosphatemia (Continued)

Correct pre-existing hypophosphatemia prior to initiating therapy with Injectafer. Monitor serum phosphate levels in patients at risk for chronic low serum phosphate. Check serum phosphate levels prior to a repeat course of treatment in patients at risk for low serum phosphate and in any patient who receives a second course of therapy within three months. Treat hypophosphatemia as medically indicated.

Second-generation IV iron products include ferumoxytol injection (Feraheme; AMAG Pharmaceuticals), ferric derisomaltose injection, solution (Monoferric; Pharmacosmos Therapeutics Inc), and ferric carboxymaltose injection (FCM) (Injectafer; Daiichi Sankyo, Inc).^{9,33-35}

Iron salts are widely used but have clinical limitations: SFG and IS can only be given in small (< 250-mg) doses, which may not replenish the average iron deficit of 1500 mg in patients of various etiologies.^{9,27,29}

Furthermore, use of first-generation IV iron formulations may be associated with increased risk of certain AEs. The prescribing information for ID includes a boxed warning for anaphylactic-type reactions.³⁰ The prescribing information for IS notes that more than 2% of adult patients in clinical trials experienced diarrhea, nausea, vomiting, headache, dizziness, hypotension, pruritus, pain in extremity, arthralgia, back pain, muscle cramp, injection site reactions, chest pain, and peripheral edema.³¹ Additionally, the prescribing information for SFG notes that more than 10% of adult patients in clinical trials experienced nausea, vomiting/diarrhea, injection site reaction, hypotension, cramps, hypertension, dizziness, abnormal erythrocytes, dyspnea, chest pain, and leg cramps and pain.³²

High-dose IV iron formulations require fewer infusions, lowering the risk of infusion-related reactions or extravasations and reducing health care resource use.²⁸ Use of these second-generation IV irons may be associated with AEs including nausea, rash, diarrhea, headache, hypertension, hypotension, flushing, injection site reactions, constipation, peripheral edema, erythema, hypophosphatemia, and dizziness.³³⁻³⁵

ABOUT INJECTAFER

FCM, a high-dose formulation of IV iron, delivers up to 1500 mg per course of treatment with 2 doses of 750 mg separated by at least 7 days.³⁵ FCM releases iron slowly so the body can absorb what it needs and store the remaining iron in the bone marrow or liver.³⁶ FCM is a colloidal iron (III) hydroxide in complex with an iron-releasing carbohydrate polymer (carboxymaltose).³⁵ In clinical trials, 0.1% (2/1775) of patients treated with FCM reported serious anaphylactic/anaphylactoid reactions and the most commonly

reported AEs among adult patients (> 2%) were nausea, hypertension, flushing, injection site reactions, erythema, hypophosphatemia, and dizziness.³⁵ Multiple administration options are approved for patients with IDA.³⁵ Generally, depending on patient body weight, it may be administered as a single dose up to 1000 mg or as 2 separate 750-mg doses separated by at least 7 days.³⁵

FCM is indicated for the treatment of IDA in adult and pediatric patients (age, ≥ 1 year) who have either intolerance or an unsatisfactory response to oral iron.³⁵ FCM also is indicated for the treatment of IDA in adult patients with NDD-CKD.³⁵ In addition, FCM is the first and only IV iron indicated for the treatment of ID in adult patients with New York Heart Association class II/III HF to improve exercise capacity.³⁵

REAL-WORLD ANALYSIS OF TOTAL COST OF CARE WITH IV IRON IN IDA

A retrospective claims analysis was conducted from a US commercial health plan perspective to compare the total cost of care per-patient-per-month between FCM and LDI or IS in patients with IDA.¹⁰ The study analyzed pharmacy and medical claims data from the IQVIA PharMetrics Plus database in patients with at least 1 claim associated with IDA who received treatment with IV iron between 2017 and 2019.¹⁰

The difference in monthly health care costs before and after IV iron treatment was calculated in patients who received 2 doses of FCM and compared with costs in patients treated with LDI (including IS, ID, and SFG); a separate subanalysis compared costs in patients treated with FCM to those in patients treated with IS.¹⁰ The total costs of care consisted of the separate categories of inpatient, emergency department, outpatient (IV iron infusion and related costs), outpatient other costs (excluding IV iron infusion and related costs), and pharmacy oral costs.¹⁰ Costs were analyzed for the overall population, as well as separately for patients diagnosed with HF, CKD, or cancer in the 6 months before their first IV iron treatment claim.¹⁰ The comorbidity subgroups were not mutually exclusive.¹⁰ Patients with a claim for dialysis, CKD stage 5, or end-stage renal disease were excluded.¹⁰ Covariates used for adjustment of the cost ratio post index analysis

IMPORTANT SAFETY INFORMATION (*Continued*) WARNINGS AND PRECAUTIONS (*Continued*)

Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving Injectafer. Patients may present with shock, clinically significant hypotension, loss of consciousness, and/or collapse. Monitor patients for signs and symptoms of hypersensitivity during and after Injectafer administration for at least 30 minutes and until clinically stable following completion of the infusion. Only administer Injectafer when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions. In clinical trials, serious anaphylactic/anaphylactoid reactions were reported in 0.1% (2/1775) of subjects receiving Injectafer. Other serious or severe adverse reactions potentially associated with hypersensitivity which included, but were not limited to, pruritus, rash, urticaria, wheezing, or hypotension were reported in 1.5% (26/1775) of these subjects.

included the pre-index monthly health care costs, patient age and gender, year of treatment index, and Charlson Comorbidity Index (or National Cancer Institute Comorbidity Index in the cancer subgroup).¹⁰

Overall Results

Overall, 37,655 patients treated with FCM and 44,237 patients treated with LDI (of which 27,461 were treated with IS) were included in the analysis.¹⁰ Among all patients with IDA, the largest increase in unadjusted mean monthly total costs from pre- to post index (6 months before index IV iron to 12 months after) was seen for those in the IS cohort, and the smallest increase was seen in the FCM cohort (Table 1).^{10,37} After adjustment for covariates, the post-index total cost (including the cost of IV iron treatment) among all patients with IDA was significantly lower for FCM than for LDI (adjusted cost ratio [ACR], 0.96) or IS (ACR, 0.92) (both, $P < .0001$) (Figure 1).¹⁰

Comorbidity Subgroup Results

The subgroup of patients with IDA and HF included 3002 patients in the FCM cohort and 3641 patients in the LDI cohort, of which 2403

were treated with IS.¹⁰ In the 12 months following IV iron treatment among patients with HF, those treated with FCM had significantly lower monthly total health care costs than those treated with LDI (ACR, 0.78) or IS (ACR, 0.75) (both, $P < .0001$) (Table 2 and Figure 2).^{10,37}

The subgroup of patients with IDA and CKD included 3727 patients in the FCM cohort and 5068 patients in the LDI cohort, of which 3489 were treated with IS.¹⁰ In the 12 months following IV iron treatment among patients with CKD, those treated with FCM had significantly lower monthly total health care costs than did those treated with LDI (ACR, 0.81) or IS (ACR, 0.79) (both, $P < .0001$) (Table 3 and Figure 3).^{10,37}

Finally, the subgroup of patients with IDA and cancer included 7829 patients in the FCM cohort and 6899 patients in the LDI cohort, of which 4086 were treated with IS.¹⁰ In the 12 months following IV iron treatment in patients with cancer, those treated with FCM had significantly lower monthly total health care costs than those treated with LDI (ACR, 0.89) or IS (ACR, 0.84) (both, $P < .0001$) (Table 4 and Figure 4).^{10,37}

Greater cost reductions were seen in chronic disease subgroups than in the overall IDA population, with the highest reduction in

Table 1. PPPM Costs Pre- and Post-Index IV Iron for All Patients With IDA^{a,37}

	Pre-Index Cost			Post-Index Cost			Cost Difference		
	FCM n = 37,655	LDI n = 44,237	IS n = 27,461	FCM	LDI	IS	FCM	LDI	IS
Inpatient	\$783.00	\$937.00	\$1010.00	\$609.00	\$906.00	\$973.00	-\$175.00	-\$31.00	-\$37.00
ED	\$65.00	\$95.00	\$97.00	\$48.00	\$73.00	\$74.00	-\$17.00	-\$22.00	-\$23.00
Outpatient (IV iron infusion-related)	—	—	—	\$216.00	\$119.00	\$132.00	\$216.00	\$119.00	\$132.00
Outpatient other	\$1166.00	\$1156.00	\$1223.00	\$1358.00	\$1370.00	\$1446.00	\$192.00	\$214.00	\$223.00
Pharmacy oral	\$355.00	\$301.00	\$316.00	\$453.00	\$373.00	\$391.00	\$98.00	\$72.00	\$76.00
Total	\$2369.00	\$2489.00	\$2645.00	\$2684.00	\$2840.00	\$3016.00	\$314.00	\$351.00	\$371.00

ED, emergency department; FCM, ferric carboxymaltose injection; IDA, iron deficiency anemia; IS, iron sucrose; IV, intravenous; LDI, low-dose IV iron therapy; PPPM, per-patient-per-month.

^aSensitivity analyses of FCM and LDI/IS patients with similar pre-index baseline costs found similar results for cost differences and post-index ACRs.

IMPORTANT SAFETY INFORMATION (Continued) WARNINGS AND PRECAUTIONS (Continued)

Hypertension

In clinical studies, hypertension was reported in 4% (67/1775) of subjects in clinical trials 1 and 2. Transient elevations in systolic blood pressure, sometimes occurring with facial flushing, dizziness, or nausea were observed in 6% (106/1775) of subjects in these two clinical trials. These elevations generally occurred immediately after dosing and resolved within 30 minutes. Monitor patients for signs and symptoms of hypertension following each Injectafer administration.

Laboratory Test Alterations

In the 24 hours following administration of Injectafer, laboratory assays may overestimate serum iron and transferrin bound iron by also measuring the iron in Injectafer.

costs (22%) seen among those with HF receiving FCM, followed by those with CKD (19%), those with cancer (11%) and the overall study cohort (4%) vs LDI; similar results were seen when comparing FCM to IS.¹⁰ The reduction in total cost of care seen with FCM treatment was mainly driven by lower inpatient and outpatient costs; the price differential due to the higher drug acquisition cost of FCM compared with LDI was offset by reductions in inpatient and outpatient costs after receiving IV iron therapy.¹⁰

Limitations

This analysis is subject to a number of limitations, as claims data are subject to coding errors, variations in reporting among different clinical practices, and missing data.¹⁰ For example, the use of concomitant over-the-counter oral iron replacement was not captured in this analysis.¹⁰ Furthermore, potential bias due to unobservable differences

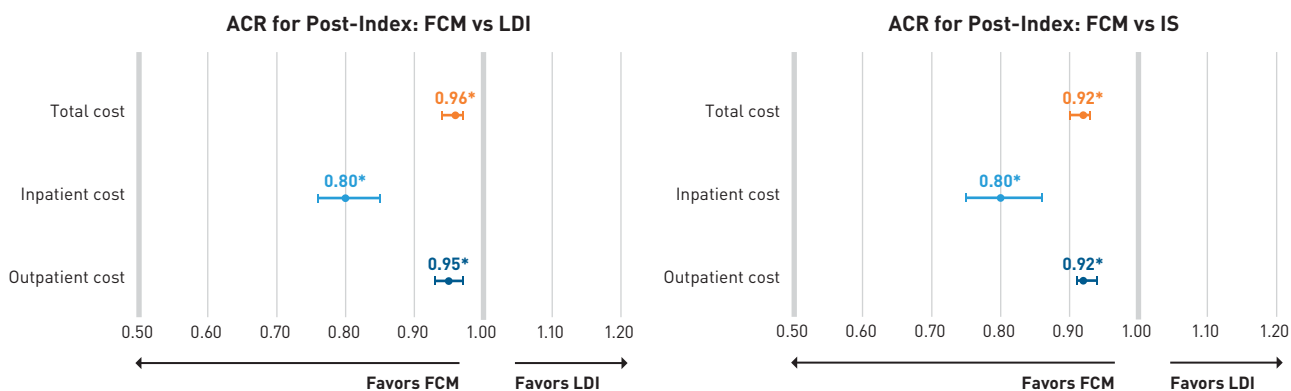
between study cohorts cannot be ruled out, and generalizability of results may be limited.¹⁰

CONCLUSIONS

Effective management of IDA via IV iron therapies is essential to improving clinical outcomes and reducing health care costs in indicated patients, especially in those with certain comorbid conditions. FCM is a high-dose IV iron formulation capable of delivering up to 1500 mg of iron in a single treatment course. A retrospective claims analysis demonstrated the economic value of FCM, showing that patients with IDA—especially those with comorbid HF, CKD, or cancer—experienced significant reductions in total monthly health care costs from pre- to post treatment compared with those receiving

Continued on page 10

Figure 1. ACR Post-Index IV Iron for All Patients With IDA¹⁰



ACR, adjusted cost ratio; FCM, ferric carboxymaltose injection; IDA, iron deficiency anemia; IS, iron sucrose; IV, intravenous; LDI, low-dose IV iron therapy.

*P < .0001

**IMPORTANT SAFETY INFORMATION (Continued)
ADVERSE REACTIONS**

Adults

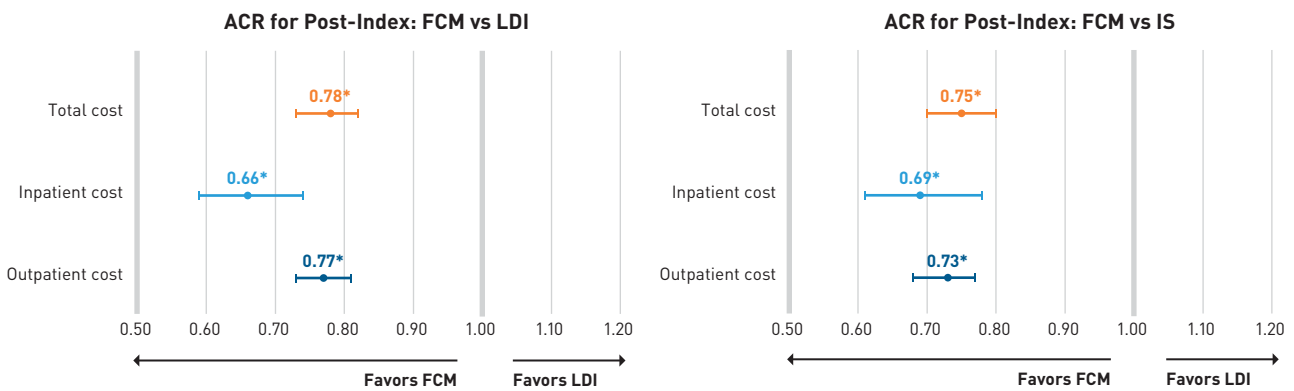
In two randomized clinical studies [Studies 1 and 2], a total of 1775 patients were exposed to Injectafer, 15 mg/kg of body weight, up to a maximum single dose of 750 mg of iron on two occasions, separated by at least 7 days, up to a cumulative dose of 1500 mg of iron. Adverse reactions reported by >2% of Injectafer-treated patients were nausea (7.2%); hypertension (4%); flushing (4%); injection site reactions (3%); erythema (3%); hypophosphatemia (2.1%); and dizziness (2.1%).

Table 2. PPPM Costs Pre- and Post-Index IV Iron for Patients With IDA and HF^{a,37}

	Pre-Index Cost			Post-Index Cost			Cost Difference		
	FCM n=3002	LDI n=3641	IS n=2403	FCM	LDI	IS	FCM	LDI	IS
Inpatient	\$2029.54	\$3100.93	\$2993.10	\$1662.46	\$2972.82	\$2798.80	-\$367.08	-\$128.11	-\$194.30
ED	\$86.59	\$152.75	\$150.37	\$71.41	\$132.29	\$125.85	-\$15.18	-\$20.46	-\$24.51
Outpatient (IV iron infusion-related)	—	—	—	\$167.81	\$103.98	\$115.85	\$167.81	\$103.98	\$115.85
Outpatient other	\$1439.45	\$1556.80	\$1539.99	\$1585.42	\$1895.95	\$1965.77	\$145.97	\$339.15	\$425.78
Pharmacy oral	\$485.06	\$589.48	\$592.55	\$593.52	\$698.88	\$684.98	\$108.46	\$109.41	\$92.43
Total	\$4040.64	\$5399.96	\$5276.01	\$4080.62	\$5803.93	\$5691.26	\$39.98	\$403.97	\$415.25

ED, emergency department; FCM, ferric carboxymaltose injection; HF, heart failure; IDA, iron deficiency anemia; IS, iron sucrose; IV, intravenous; LDI, low-dose IV iron therapy; PPPM, per-patient-per-month.

^aSensitivity analyses of FCM and LDI/IS patients with similar pre-index baseline costs found similar results for cost differences and post-index ACRs.

Figure 2. ACR Post-Index IV Iron for Patients With IDA and HF¹⁰

ACR, adjusted cost ratio; FCM, ferric carboxymaltose injection; HF, heart failure; IDA, iron deficiency anemia; IS, iron sucrose; IV, intravenous; LDI, low-dose IV iron therapy.

* $P < .0001$

IMPORTANT SAFETY INFORMATION (Continued)

ADVERSE REACTIONS (Continued)

Pediatric

The safety of Injectafer in pediatric patients was evaluated in Study 3. Study 3 was a randomized, active-controlled study in which 40 patients (1 to 12 years of age: 10 patients, 12 to 17 years of age: 30 patients) received Injectafer 15 mg/kg to a maximum single dose of 750 mg (whichever was smaller) on Days 0 and 7 for a maximum total dose of 1500 mg; 38 patients evaluable for safety in the control arm received an age-dependent formulation of oral ferrous sulfate for 28 days. The median age of patients who received Injectafer was 14.5 years (range, 1-17); 83% were female; 88% White and 13% Black. The most common adverse reactions ($\geq 4\%$) were hypophosphatemia (13%), injection site reactions (8%), rash (8%), headache (5%), and vomiting (5%).

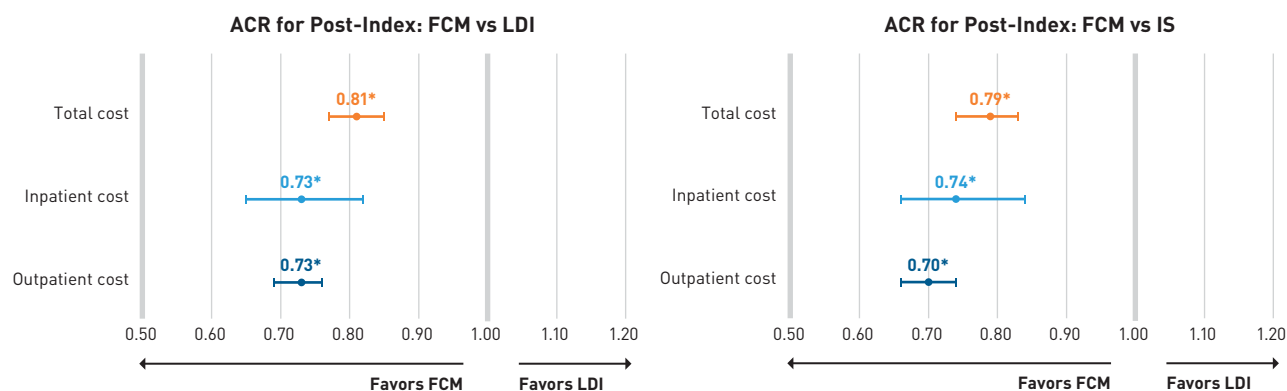
Table 3. PPPM Costs Pre- and Post-Index IV Iron for Patients With IDA and CKD^{a,37}

	Pre-Index Cost			Post-Index Cost			Cost Difference		
	FCM n=3727	LDI n=5068	IS n=3489	FCM	LDI	IS	FCM	LDI	IS
Inpatient	\$2029.54	\$3100.93	\$2993.10	\$1662.46	\$2972.82	\$2798.80	-\$367.08	-\$128.11	-\$194.30
ED	\$86.59	\$152.75	\$150.37	\$71.41	\$132.29	\$125.85	-\$15.18	-\$20.46	-\$24.51
Outpatient (IV iron infusion-related)	—	—	—	\$167.81	\$103.98	\$115.85	\$167.81	\$103.98	\$115.85
Outpatient other	\$1439.45	\$1556.80	\$1539.99	\$1585.42	\$1895.95	\$1965.77	\$145.97	\$339.15	\$425.78
Pharmacy oral	\$485.06	\$589.48	\$592.55	\$593.52	\$698.88	\$684.98	\$108.46	\$109.41	\$92.43
Total	\$4040.64	\$5399.96	\$5276.01	\$4080.62	\$5803.93	\$5691.26	\$39.98	\$403.97	\$415.25

CKD, chronic kidney disease; ED, emergency department; FCM, ferric carboxymaltose injection; IDA, iron deficiency anemia; IS, iron sucrose; IV, intravenous; LDI, low-dose IV iron therapy; PPPM, per-patient-per-month.

^aSensitivity analyses of FCM and LDI/IS patients with similar pre-index baseline costs found similar results for cost differences and post-index ACRs.

Figure 3. ACR Post-Index IV Iron for Patients With IDA and CKD¹⁰



ACR, adjusted cost ratio; CKD, chronic kidney disease; FCM, ferric carboxymaltose injection; IDA, iron deficiency anemia; IS, iron sucrose; IV, intravenous; LDI, low-dose IV iron therapy.

*P < .0001

IMPORTANT SAFETY INFORMATION (Continued)

ADVERSE REACTIONS (Continued)

Patients with Iron Deficiency and Heart Failure

The safety of Injectafer was evaluated in adult patients with iron deficiency and heart failure in randomized controlled trials FAIR-HF (NCT00520780), CONFIRM-HF (NCT01453608) and AFFIRM-AHF (NCT02937454) in which 1016 patients received Injectafer versus 857 received placebo. The overall safety profile of Injectafer was consistent across the studied indications.

Post-Marketing Experience

The following adverse reactions have been identified during post approval use of Injectafer. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

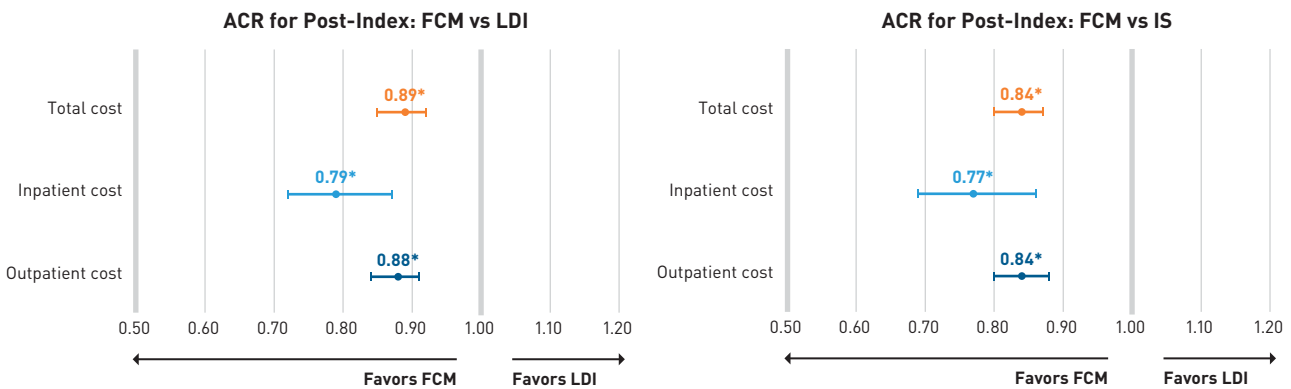
Table 4. PPPM Costs Pre- and Post-Index IV Iron for Patients With IDA and Cancer^{a,37}

	Pre-Index Cost			Post-Index Cost			Cost Difference		
	FCM n = 7829	LDI n = 6899	IS n = 4086	FCM	LDI	IS	FCM	LDI	IS
Inpatient	\$1652.25	\$1966.40	\$2133.74	\$1168.80	\$1692.90	\$1824.41	-\$483.45	-\$273.50	-\$309.33
ED	\$65.22	\$91.25	\$94.52	\$53.85	\$81.12	\$82.10	-\$11.37	-\$10.13	-\$12.41
Outpatient (IV iron infusion-related)	—	—	—	\$197.87	\$124.85	\$141.25	\$197.87	\$124.85	\$141.25
Outpatient other	\$2613.74	\$2749.24	\$3022.85	\$3363.45	\$3698.86	\$3909.29	\$749.71	\$949.63	\$886.44
Pharmacy oral	\$580.82	\$560.85	\$621.00	\$811.57	\$769.05	\$863.01	\$230.75	\$208.20	\$242.01
Total	\$4912.03	\$5367.74	\$5872.10	\$5595.54	\$6366.78	\$6820.06	\$683.51	\$999.04	\$947.96

ED, emergency department; FCM, ferric carboxymaltose injection; IDA, iron deficiency anemia; IS, iron sucrose; IV, intravenous; LDI, low-dose IV iron therapy; PPPM, per-patient-per-month.

^aSensitivity analyses of FCM and LDI/IS patients with similar pre-index baseline costs found similar results for cost differences and post-index ACRs.

Figure 4. ACR Post-Index IV Iron for Patients With IDA and Cancer¹⁰



ACR, adjusted cost ratio; FCM, ferric carboxymaltose injection; IDA, iron deficiency anemia; IS, iron sucrose; IV, intravenous; LDI, low-dose IV iron therapy.

*P < .0001

IMPORTANT SAFETY INFORMATION (Continued)

ADVERSE REACTIONS (Continued)

Post-Marketing Experience (Continued)

The following adverse reactions have been reported from the post-marketing spontaneous reports with Injectafer: *cardiac disorders*: tachycardia; *general disorders and administration site conditions*: chest discomfort, chills, pyrexia; *metabolism and nutrition disorders*: hypophosphatemia; *musculoskeletal and connective tissue disorders*: arthralgia, back pain, hypophosphatemic osteomalacia; *nervous system disorders*: syncope; *respiratory, thoracic and mediastinal disorders*: dyspnea; *skin and subcutaneous tissue disorders*: angioedema, erythema, pruritus, urticaria; *pregnancy*: fetal bradycardia.

Continued from page 6

LDI or IS. This reduction in costs was observed across key health care metrics, including inpatient costs and outpatient costs, highlighting the cost-effectiveness of FCM in patients with IDA. Payers and managed care decision-makers should consider the long-term cost benefits of optimizing IV iron therapy to improve patient outcomes and lower overall health care expenditures. As health care systems increasingly focus on value-based care, the clinical and economic benefits of FCM underscore its role as a preferred IV iron formulation in the treatment landscape for IDA, particularly in high-risk populations. •

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IMPORTANT SAFETY INFORMATION (Continued) CLINICAL CONSIDERATIONS IN PREGNANCY

Untreated IDA in pregnancy is associated with adverse maternal outcomes such as postpartum anemia. Adverse pregnancy outcomes associated with IDA include increased risk for preterm delivery and low birth weight.

Severe adverse reactions, including circulatory failure (severe hypotension, shock including in the context of anaphylactic reaction) may occur in pregnant women with parenteral iron products (such as Injectafer) which may cause fetal bradycardia, especially during the second and third trimester.

You are encouraged to report Adverse Drug Events to American Regent, Inc. at 1-800-734-9236 or to the FDA by visiting www.fda.gov/medwatch or calling 1-800-FDA-1088.

IMPORTANT SAFETY INFORMATION

INDICATIONS

Injectafer® (ferric carboxymaltose injection) is indicated for the treatment of iron deficiency anemia (IDA) in adult and pediatric patients 1 year of age and older who have either intolerance or an unsatisfactory response to oral iron, and in adult patients who have non-dialysis dependent chronic kidney disease. Injectafer is also indicated for iron deficiency in adult patients with heart failure and New York Heart Association class II/III to improve exercise capacity.

CONTRAINDICATIONS

Injectafer is contraindicated in patients with hypersensitivity to Injectafer or any of its inactive components.

WARNINGS AND PRECAUTIONS

Symptomatic Hypophosphatemia

Symptomatic hypophosphatemia with serious outcomes including osteomalacia and fractures requiring clinical intervention has been reported in patients treated with Injectafer in the post-marketing setting. These cases have occurred mostly after repeated exposure to Injectafer in patients with no reported history of renal impairment. However, symptomatic hypophosphatemia has been reported after one dose. Possible risk factors for hypophosphatemia include a history of gastrointestinal disorders associated with malabsorption of fat-soluble vitamins or phosphate, inflammatory bowel disease, concurrent or prior use of medications that affect proximal renal tubular function, hyperparathyroidism, vitamin D deficiency, malnutrition, and hereditary hemorrhagic telangiectasia (HHT or Osler-Weber-Rendu syndrome). In most cases, hypophosphatemia resolved within three months.

Symptomatic Hypophosphatemia (Continued)

Correct pre-existing hypophosphatemia prior to initiating therapy with Injectafer. Monitor serum phosphate levels in patients at risk for chronic low serum phosphate. Check serum phosphate levels prior to a repeat course of treatment in patients at risk for low serum phosphate and in any patient who receives a second course of therapy within three months. Treat hypophosphatemia as medically indicated.

Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving Injectafer. Patients may present with shock, clinically significant hypotension, loss of consciousness, and/or collapse. Monitor patients for signs and symptoms of hypersensitivity during and after Injectafer administration for at least 30 minutes and until clinically stable following completion of the infusion. Only administer Injectafer when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions. In clinical trials, serious anaphylactic/anaphylactoid reactions were reported in 0.1% (2/1775) of subjects receiving Injectafer. Other serious or severe adverse reactions potentially associated with hypersensitivity which included, but were not limited to, pruritus, rash, urticaria, wheezing, or hypotension were reported in 1.5% (26/1775) of these subjects.

Hypertension

In clinical studies, hypertension was reported in 4% (67/1775) of subjects in clinical trials 1 and 2. Transient elevations in systolic blood pressure, sometimes occurring with facial flushing, dizziness, or nausea were observed in 6% (106/1775) of subjects in these two clinical trials. These elevations generally occurred immediately after dosing and resolved within 30 minutes. Monitor patients for signs and symptoms of hypertension following each Injectafer administration.

Laboratory Test Alterations

In the 24 hours following administration of Injectafer, laboratory assays may overestimate serum iron and transferrin bound iron by also measuring the iron in Injectafer.

ADVERSE REACTIONS

Adults

In two randomized clinical studies [Studies 1 and 2], a total of 1775 patients were exposed to Injectafer, 15 mg/kg of body weight, up to a maximum single dose of 750 mg of iron on two occasions, separated by at least 7 days, up to a cumulative dose of 1500 mg of iron. Adverse reactions reported by >2% of Injectafer-treated patients were nausea (7.2%); hypertension (4%); flushing (4%); injection site reactions (3%); erythema (3%); hypophosphatemia (2.1%); and dizziness (2.1%).

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IMPORTANT SAFETY INFORMATION (*Continued*) ADVERSE REACTIONS (*Continued*)

Pediatric

The safety of Injectafer in pediatric patients was evaluated in Study 3. Study 3 was a randomized, active-controlled study in which 40 patients (1 to 12 years of age: 10 patients, 12 to 17 years of age: 30 patients) received Injectafer 15 mg/kg to a maximum single dose of 750 mg (whichever was smaller) on Days 0 and 7 for a maximum total dose of 1500 mg; 38 patients evaluable for safety in the control arm received an age-dependent formulation of oral ferrous sulfate for 28 days. The median age of patients who received Injectafer was 14.5 years (range, 1-17); 83% were female; 88% White and 13% Black. The most common adverse reactions ($\geq 4\%$) were hypophosphatemia (13%), injection site reactions (8%), rash (8%), headache (5%), and vomiting (5%).

Patients with Iron Deficiency and Heart Failure

The safety of Injectafer was evaluated in adult patients with iron deficiency and heart failure in randomized controlled trials FAIR-HF (NCT00520780), CONFIRM-HF (NCT01453608) and AFFIRM-AHF (NCT02937454) in which 1016 patients received Injectafer versus 857 received placebo. The overall safety profile of Injectafer was consistent across the studied indications.

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