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Injectafer for First-Line Treatment of IDA in NDD-CKD

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The Interplay Between IDA and CKD

Non–dialysis-dependent chronic kidney disease (NDD-CKD) is a common condition in primary care patients. The prevalence of CKD in the United States is 14.8% in the general population and has remained largely unchanged over the past 2 decades.[1] Early stages of NDD-CKD are frequently under- or misdiagnosed.[1,2] Although 90% of Medicare patients see their primary care physician in the year following a CKD diagnosis, only 26% see a nephrologist.[1]

Anemia is a common condition in patients with NDD-CKD, with iron deficiency (ID) being the most common reversible cause of anemia in this patient population.[3-6] Iron metabolism is tightly regulated through intake of exogenous iron and iron release from recycling macrophages and hepatocytes.[3,4] In healthy individuals, the total body iron content is approximately 3 to 4 g in addition to 1 to 2 mg daily absorption of exogenous iron.[4] The daily requirement to support erythropoiesis is 25 mg, which is primarily obtained from iron recycling.[4] The progression of CKD and loss of renal function can have a deleterious effect on iron physiology and these patients require more daily iron than healthy individuals to increase the levels of circulating iron.[3,4,6] Multiple factors in patients with decreased kidney function can lead to increased iron utilization, including chronic inflammation, blood loss, malabsorption of iron, and dietary inadequacy.[4,7-9] The increased inflammatory state of patients with CKD results in elevated levels of hepcidin, which inhibits release of iron from reticuloendothelial macrophages and hepatocytes into plasma.[3,4,10,11] The elevated levels of hepcidin block or inhibit iron absorption in the gut, resulting in iron release by macrophages.[3,8,11] This increase in iron utilization can lead to iron deficiency anemia (IDA) if the total iron levels continue to decline.[3,8,11] Absolute and functional ID have distinct causes, and distinguishing between the 2 is important before making treatment decisions.[3,8,11] Functional ID occurs when iron stores cannot be mobilized quickly enough for the production of new red blood cells (RBCs), despite the availability of adequate iron within the body.[11-13] Functional ID may occur during periods of heightened erythropoiesis and often will lead to anemia of chronic disease, which can occur on its own, but also may coexist with IDA.[11,13,14] Absolute ID is characterized by extremely reduced or absent iron stores in bone marrow, liver, and the spleen.[11,13,15] In absolute ID, iron stores are not sufficient enough to support normal RBC production.[11]

There is a higher prevalence of ID and anemia in individuals with NDD-CKD than in those with normal kidney function.[7,12,16,17] Research based on National Health and Nutrition Examination Survey (NHANES) III data, plus subsequent NHANES 2-year data sets, found that about 58% of men and 70% to 73% of women with CKD are at higher risk for ID.[16] Additionally, the prevalence of anemia and ID increases as kidney function declines.[4,17,18] In one study, the prevalence of anemia increased from 1% among patients with an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m^2 to 9% at an eGFR of 30 mL/min/1.73 m^2 and to 33% to 67% at an eGFR of 15 mL/min/1.73 m^2.[19]

Recognizing IDA in Patients With CKD

The signs and symptoms of IDA may include headache, fatigue, weakness, brittle nails, shortness of breath, cold sensitivity in hands and feet, dizziness, lightheadedness, and pica.[3,7,20] Identifying IDA in patients with CKD can be challenging, as some symptoms of IDA, including fatigue, weakness, and restless legs syndrome, can overlap with those of other conditions and may mirror those of CKD.[3,7,21] Additionally, the severity of these symptoms can vary depending on the extent of iron depletion.[7] Patients with mild to moderate IDA may not exhibit any signs.[3,7] The severity of these signs can range from mild to severe.[3,7]

Guidelines from Kidney Disease Improving Global Outcomes (KDIGO) recommend screening for anemia at diagnosis of patients with CKD.[6] The frequency of monitoring varies, based on the presence of anemia on initial evaluation,[6] whether patients are treated with erythropoietin-stimulating agents (ESAs), and on the severity of CKD.[6] In patients without anemia, hemoglobin (Hb) concentration should be measured when clinically indicated and at least every 12 months in patients with stage 3 CKD, every 6 months in stage 4 to 5 NDD-CKD, and every 3 months in

TABLE 1 Iron parameters for diagnosing IDA in NDD-CKD[6,22-24]*

Key Blood Tests	Normal Range for Men	Normal Range for Nonpregnant Women	IDA†
Hb (g/dL)	>13	>12	Low
TSAT (%)	20–50	20–50	≤30%
Serum ferritin (mcg/L)	40–300	20–200	<10
TIBC (mcg/dL)	60–170	60–170	Higher than normal

CKD=chronic kidney disease; ESA=erythropoietin-stimulating agent; Hb=hemoglobin; IDA=iron deficiency anemia; NDD-CKD=non–dialysis-dependent chronic kidney disease; TIBC=total iron-binding capacity; TSAT=transferrin saturation.

*The numbers represent common measurements for results of these tests. Normal value ranges may vary slightly among different laboratories.
†Adult patients with CKD (>15 years of age) and anemia not on iron or ESA therapy.

stage 5 hemodialysis (HD)-CKD and in stage 5 peritoneal dialysis (PD)-CKD.[6] In patients already diagnosed with anemia who are not being treated with ESAs, Hb assessment should be done when clinically indicated and at least every month for those with stage 5 HD-CKD and at least every 3 months for stages 3 to 5 NDD-CKD and in stage 5 PD-CKD.[6]

The initial evaluation of IDA is the same for patients with NDD-CKD as for individuals with normal kidney function, although there are unique cutoff values for those with CKD.[3,6] **Table 1** illustrates iron parameters used to diagnose IDA in NDD-CKD. The KDIGO guidelines recommend evaluation of Hb concentration as the first step in determining whether a patient has anemia.[6] If Hb levels are ≥13 g/dL in men or ≥12 g/dL in women, then the patient does not have anemia but may have ID. Additional evaluation is recommended to determine cause of anemia for patients with CKD and Hb <13 or <12 g/dL, depending on sex.[3,6] Confirmation of IDA consists of measurements of serum ferritin and transferrin saturation (TSAT).[3,6] Total iron-binding capacity, which measures the availability of iron to support erythropoiesis, is an additional diagnostic test that can be used to verify IDA.[24,25]

Currently, there is no consensus or agreed-upon guideline for cutoff values that define IDA in chronic inflammatory conditions such as NDD-CKD.[3,6] As kidney disease progresses, anemia increases in prevalence.[12] TSAT often is used to measure the availability of iron to support erythropoiesis.[6] Serum ferritin is the most widely used diagnostic measure to evaluate iron storage.[6] However, it should be noted that serum ferritin can be elevated in the presence of inflammation, and therefore IDA may still be present when serum ferritin is within the normal range.[3] Therefore, experts recommend that if serum ferritin is between 100 and 300 mcg/L, a TSAT test should be performed to confirm iron deficiency.[4] Serum ferritin and TSAT often are used together to confirm iron status.[3,4,6] Collaboration with colleagues in hematology and nephrology may be helpful in performing diagnostic tests to confirm ID and IDA.

First-Line Treatment of IDA With IV Iron

IDA is the most common reversible cause of chronic or worsening anemia in patients with CKD other than anemia related directly to CKD.[6] IDA in patients with NDD-CKD is treatable with intravenous (IV) iron replacement.[26] IDA treatment goals are to increase Hb, serum ferritin, and TSAT and to help restore iron levels.[6] KDIGO guidelines for managing anemia recommend a trial of IV iron or a 1- to 3-month trial of oral iron to restore Hb concentrations without starting ESA treatment in patients whose TSAT is ≤30% and whose ferritin is ≤500 ng/mL.[6] For patients on ESA therapy, the treatment target is an increase in Hb concentration or a decrease in required ESA dose.[6]

IV iron treatment ensures that 100% of iron is delivered into the patient's bloodstream to be used in production of Hb or stored as ferritin for future use when Hb is depleted.[27,28] Several IV iron preparations are indicated for treatment of NDD-CKD in the United States, including ferric carboxymaltose (FCM).[26] Not all IV irons are the same. Historically, dextran products have been associated with an increased risk for anaphylaxis.[6,29] The most severe risk for anaphylaxis has been related to high-molecular-weight iron dextran products, now no longer available.[29] Today, there are multiple options including dextran-free formulations.[11,26,30-33]

Injectafer® Is FDA-Approved as a First-Line Treatment for IDA in Patients With NDD-CKD[26]

Injectafer® (ferric carboxymaltose injection) is a dextran-free* iron replacement product approved by the US Food and Drug Administration (FDA) in 2013 for the treatment of IDA in adults with intolerance to oral iron or for those who have had unsatisfactory response to oral iron or those with NDD-CKD.[26]

The carboxymaltose shell of Injectafer® is tightly bound around an iron core.[26,34] The structure is similar to physiologic ferritin.[34] Clinically, the molecular structure is important because it enables Injectafer® to provide a large amount of iron in a controlled fashion.[28] After administration, enzymes in the blood partially degrade the Injectafer® carbohydrate shell.[27,34] Injectafer® is then likely taken up by macrophages of the reticuloendothelial system, where enzymes continue breaking down the carbohydrate shell.[27,28,34] This slow and gradual release of iron prevents the transferrin available for uptake from becoming fully saturated with iron and results in controlled release of iron into the bloodstream.[28,34]

The efficacy and safety of Injectafer® has been demonstrated in 2 pivotal clinical trials.[35,36] Here, we discuss the REPAIR-IDA trial, which was the first and largest head-to-head IV iron study in

*In Injectafer® clinical trials, serious anaphylactic/anaphylactoid reactions were reported in 0.1% (2 of 1775) of patients receiving Injectafer®.

Injectafer® (ferric carboxymaltose injection) is indicated for the treatment of iron deficiency anemia (IDA) in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron, or who have non-dialysis dependent chronic kidney disease. Injectafer® is contraindicated in patients with hypersensitivity to Injectafer® or any of its inactive components.

Please see accompanying Full Prescribing Information.

patients with IDA and NDD-CKD. REPAIR-IDA was a randomized, active-controlled, multicenter, noninferiority, open-label trial comparing the safety and efficacy of Injectafer® with IV iron sucrose in 2584 adult patients with IDA (Hb ≤11.5 g/dL) and NDD-CKD.[35,36] The primary endpoint was mean change from baseline Hb to highest observed Hb at any time between baseline and end of treatment period (Day 56) or time of intervention.[35,36] The primary composite safety endpoint was the proportion of patients experiencing at least one treatment-emergent adverse event including all-cause death, nonfatal myocardial infarction, nonfatal stroke, unstable angina requiring hospitalization, congestive heart failure, cardiac arrhythmia, and hyper- or hypotensive events.[35,36]

Table 2 shows the patient characteristics that were balanced between arms in the REPAIR-IDA trial. As with the other Injectafer® pivotal trial, REPAIR-IDA did not exclude patients with multiple comorbidities, or those with a history of iron intolerance or drug allergies (with the exception of known hypersensitivity to study treatments).[35,36]

Controlled release of Injectafer® allows for dosing that does not require weight-based calculations in patients weighing ≥50 kg (110 lb).[26] For adult patients weighing <50 kg, Injectafer® should be given as 15 mg/kg body weight for a total cumulative dose not to exceed 1500 mg of iron per course of treatment.[26] Injectafer® is administered via IV push over 7.5 minutes per dose or via a slow infusion protocol of at least 15 minutes per infusion.[26] For patients who weigh ≥50 kg, two 750-mg doses are given at least 7 days apart, making it the only FDA-approved IV iron that delivers up to 1500 mg in a single treatment course.[26] Injectafer® treatment may be repeated if IDA reoccurs. Monitor serum phosphate levels in patients at risk for low serum phosphate who require a repeat course of treatment (see Important Safety Information).[26] The maximum cumulative dose of Injectafer® is 1500 mg per course of treatment.[26] These results confirm that Injectafer® is an effective and well-tolerated first-line IDA treatment choice for adult patients with NDD-CKD.[35]

TABLE 2 Patient characteristics at baseline in REPAIR-IDA[36]

	Injectafer® (n=1276)	Iron sucrose (n=1285)
Age, mean (SD), years	67.5 (13%)	67.2 (13%)
CKD stage 3-4	1113 (87.2%)	1105 (86%)
Female	810 (63.5%)	818 (63.7%)
ESA use	230 (18%)	228 (17.7%)
History of iron intolerance	67 (5.3%)	63 (4.9%)
History of drug allergy	571 (44.7%)	587 (45.7%)
History of CHF	315 (24.7%)	309 (24%)
History of MI	197 (15.4%)	184 (14.3%)
History of stroke	165 (12.9%)	157 (12.2%)

CHF=congestive heart failure; CKD=chronic kidney disease; ESA=erythropoietin-stimulating agent; MI=myocardial infarction; SD=standard deviation.

In this study, Injectafer® achieved the primary endpoint and demonstrated greater absolute increase in Hb improvement (**Figure 1**).[36] The mean Hb increase was 1.13 g/dL in the Injectafer® group compared with 0.92 g/dL in the iron sucrose group (95% CI, 0.13–0.28).[35] Additionally, Injectafer® showed greater improvements in ferritin and TSAT than iron sucrose.[36]

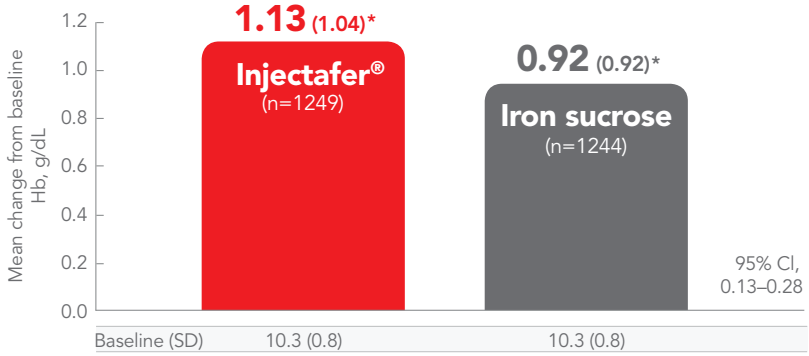
The mean increases in ferritin, TSAT, and serum iron from the baseline to the highest value by Day 56 also were significantly greater in the FCM group than in the iron sucrose group (**Figure 2**).[35,36]

There was no significant difference between Injectafer® and IV iron sucrose for the primary composite safety endpoint.[36] In clinical trials, serious anaphylactic/anaphylactoid reactions were reported in 0.1% (2 of 1775) of patients receiving Injectafer®.[26] In a post hoc analysis from the REPAIR-IDA trial, 142 patients (11.1%) receiving 1000 mg of iron sucrose required re-treatment versus the 71 patients (5.6%) receiving 1500 mg of Injectafer®.[37] According to 7 Injectafer® clinical studies, IDA patients had average calculated iron deficits of approximately 1500 mg.[37]

Injectafer® Worldwide Experience

Injectafer® was approved by the FDA in 2013 and has been used extensively in clinical practice with more than 1 million patients treated in the United States.[26,38] Built on a solid foundation of clinical evidence, Injectafer® is the most studied IV iron with more than 40 clinical trials including 8800 patients across the spectrum of IDA etiologies.[38] Injectafer® has been approved in 76 countries.[38] In all, worldwide treatment experience with Injectafer® exceeds 12 million patient-years.[38] Clinical trial data and real-world experience have proven that Injectafer® is a safe and effective first-line treatment for IDA in patients with NDD-CKD.[26,35]

FIGURE 1 REPAIR-IDA met the primary efficacy endpoint.[36]
Hb: Mean change from baseline to highest value between baseline and Day 56 or time of intervention

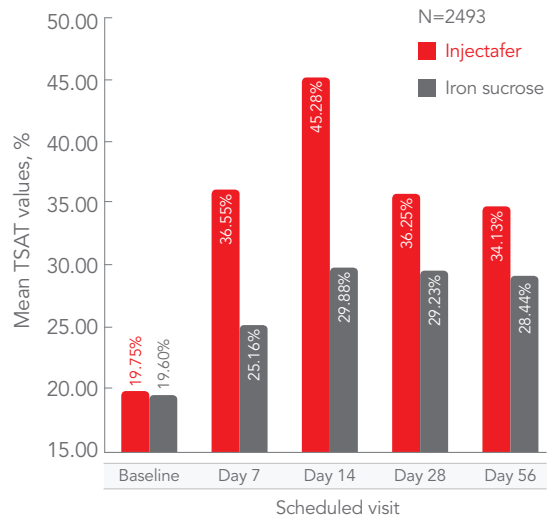


CI=confidence interval; Hb=hemoglobin; SD=standard deviation.
*SD.
The mean increase in Hb was 1.13 in the Injectafer® (ferric carboxymaltose injection) group and 0.92 in the iron sucrose group, thus demonstrating the noninferiority of Injectafer® to iron sucrose.

FIGURE 2 Mean changes from baseline to highest observed ferritin and TSAT between baseline and Day 56.[36]

Ferritin: Mean value at each scheduled visit

TSAT: Mean value at each scheduled visit



TSAT=transferrin saturation.

INDICATIONS

Injectafer® (ferric carboxymaltose injection) is indicated for the treatment of iron deficiency anemia (IDA) in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron, or who have non-dialysis dependent chronic kidney disease.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Symptomatic hypophosphatemia requiring clinical intervention has been reported in patients at risk of low serum phosphate in the postmarketing setting. These cases have occurred mostly after repeated exposure to Injectafer in patients with no reported history of renal impairment. Possible risk factors for hypophosphatemia include a history of gastrointestinal disorders associated with malabsorption of fat-soluble vitamins or phosphate, concurrent or prior use of medications that affect proximal renal tubular function, hyperparathyroidism, vitamin D deficiency and malnutrition. In most cases, hypophosphatemia resolved within three months.

Monitor serum phosphate levels in patients at risk for low serum phosphate who require a repeat course of treatment.

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.

In clinical studies, hypertension was reported in 3.8% (67/1775) of subjects. Transient elevations in systolic blood pressure, sometimes occurring with facial flushing, dizziness, or nausea were observed in 6% (106/1775) of subjects. These elevations generally occurred immediately after dosing and resolved within 30 minutes. Monitor patients for signs and symptoms of hypertension following each Injectafer administration.

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

In two randomized clinical studies, a total of 1775 patients were exposed to Injectafer, 15 mg/kg of body weight, up to a single maximum 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 (3.8%); flushing/hot flush (3.6%); blood phosphorus decrease (2.1%); and dizziness (2.0%).

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.

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 (rarely reported event); *nervous system disorders*: syncope; *respiratory, thoracic and mediastinal disorders*: dyspnea; *skin and subcutaneous tissue disorders*: angioedema, erythema, pruritus, urticaria.

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.

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Please see accompanying Full Prescribing Information.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Injectafer safely and effectively. See full prescribing information for Injectafer.

INJECTAFER® (ferric carboxymaltose injection), for intravenous use
Initial U.S. Approval: 2013

RECENT MAJOR CHANGES

- Warnings and Precautions, Symptomatic Hypophosphatemia. (5.2) 02/2020

INDICATIONS AND USAGE

Injectafer is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients:

- who have intolerance to oral iron or have had unsatisfactory response to oral iron, **or**
- who have non-dialysis dependent chronic kidney disease.

DOSAGE AND ADMINISTRATION

For patients weighing 50 kg (110 lb) or more: Give Injectafer in two doses separated by at least 7 days. Give each dose as 750 mg for a total cumulative dose of 1500 mg of iron per course.

For patients weighing less than 50 kg (110 lb): Give Injectafer in two doses separated by at least 7 days and give each dose as 15 mg/kg body weight.

Injectafer treatment may be repeated if iron deficiency anemia reoccurs. (2)

DOSAGE FORMS AND STRENGTHS

Injection: 750 mg iron / 15 mL single-dose vial. (3)

CONTRAINDICATIONS

Hypersensitivity to Injectafer or any of its inactive components. (4)

WARNINGS AND PRECAUTIONS

- **Hypersensitivity reactions:** Observe for signs and symptoms of hypersensitivity during and after Injectafer administration for at least 30 minutes and until clinically stable following completion of each administration. (5.1)
- **Symptomatic Hypophosphatemia:** Monitor serum phosphate levels in patients at risk for low serum phosphate who require a repeat course of treatment. (5.2)
- **Hypertension:** Monitor patients closely for signs and symptoms of hypertension following each Injectafer administration. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (≥2%) are nausea, hypertension, flushing, hypophosphatemia, and dizziness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact American Regent at 1-800-734-9236 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

USE IN SPECIFIC POPULATIONS

Lactation: Monitor breastfed infants for gastrointestinal toxicity. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 02/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Injectafer is indicated for the treatment of iron deficiency anemia in adult patients:

- who have intolerance to oral iron or have had unsatisfactory response to oral iron, **or**
- who have non-dialysis dependent chronic kidney disease.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Recommended dosage for patients weighing 50 kg (110 lb) or more: Give Injectafer in two doses separated by at least 7 days. Give each dose as 750 mg for a total cumulative dose not to exceed 1500 mg of iron per course.

Recommended dosage for patients weighing less than 50 kg (110 lb): Give Injectafer in two doses separated by at least 7 days. Give each dose as 15 mg/kg body weight for a total cumulative dose not to exceed 1500 mg of iron per course.

Each mL of Injectafer contains 50 mg of elemental iron.

2.2 Preparation and Administration

Administer Injectafer intravenously, either as an undiluted slow intravenous push or by infusion. When administered via infusion, dilute up to 750 mg of iron in no more than 250 mL of sterile 0.9% sodium chloride injection, USP, such that the concentration of the infusion is not less than 2 mg of iron per mL and administer over at least 15 minutes.

When added to an infusion bag containing 0.9% sodium chloride injection, USP, at concentrations ranging from 2 mg to 4 mg of iron per mL, Injectafer solution is physically and chemically stable for 72 hours when stored at room temperature. To maintain stability, do not dilute to concentrations less than 2 mg iron/mL.

Inspect parenteral drug products visually for the absence of particulate matter and discoloration prior to administration. The product contains no preservatives. Each vial of Injectafer is intended for single-dose only.

When administering as a slow intravenous push, give at the rate of approximately 100 mg (2 mL) per minute. Avoid extravasation of Injectafer since brown discoloration of the extravasation site may be long lasting. Monitor for extravasation. If extravasation occurs, discontinue the Injectafer administration at that site.

Discard unused portion.

2.3 Repeat Treatment Monitoring Safety Assessment

Injectafer treatment may be repeated if iron deficiency anemia reoccurs. Monitor serum phosphate levels in patients at risk for low serum phosphate who require a repeat course of treatment *[see Warnings and Precautions (5.2)]*.

3 DOSAGE FORMS AND STRENGTHS

Injection: 750 mg iron / 15 mL single-dose vial.

4 CONTRAINDICATIONS

Injectafer is contraindicated in patients with a history of hypersensitivity to Injectafer or any of its components [see *Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 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. *[see Adverse Reactions (6.1, 6.2)]*. 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 not limited to, pruritus, rash, urticaria, wheezing, or hypotension were reported in 1.5% (26/1775) of these subjects.

5.2 Symptomatic Hypophosphatemia
Symptomatic hypophosphatemia requiring clinical intervention has been reported in patients at risk of low serum phosphate in the postmarketing setting. These cases have occurred mostly after repeated exposure to Injectafer in patients with no reported history of renal impairment. Possible risk factors for hypophosphatemia include a history of gastrointestinal disorders associated with malabsorption of fat-soluble vitamins or phosphate, concurrent or prior use of medications that affect proximal renal tubular function, hyperparathyroidism, vitamin D deficiency and malnutrition. In most cases, hypophosphatemia resolved within three months.

Monitor serum phosphate levels in patients at risk for low serum phosphate who require a repeat course of treatment. *[see Dosage and Administration (2.3)]*.

5.3 Hypertension
In clinical studies, hypertension was reported in 3.8% (67/1,775) 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% (106/1,775) 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 [*see Dosage and Administration (2)*].

5.4 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.

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:
- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
- Hypophosphatemia *[see Warnings and Precautions (5.2)]*
- Hypertension *[see Warnings and Precautions (5.3)]*
- Laboratory Test Alterations *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.

In two randomized clinical studies [Studies 1 and 2, *see Clinical Studies (14)*], a total of 1,775 patients were exposed to Injectafer 15 mg/kg 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 ≥1% of treated patients are shown in the following table.

Table 1. Adverse reactions reported in ≥1% of Study Patients in Clinical Trials 1 and 2

Term	Injectafer (N=1775) %	Pooled Comparators[a] (N=1783) %	Oral iron (N=253) %
Nausea	7.2	1.8	1.2
Hypertension	3.8	1.9	0.4
Flushing/Hot Flush	3.6	0.2	0.0
Blood Phosphorus Decrease	2.1	0.1	0.0
Dizziness	2.0	1.2	0.0
Vomiting	1.7	0.5	0.4
Injection Site Discoloration	1.4	0.3	0.0
Headache	1.2	0.9	0.0
Alanine Aminotransferase Increase	1.1	0.2	0.0
Dysgeusia	1.1	2.1	0.0
Hypotension	1.0	1.9	0.0
Constipation	0.5	0.9	3.2

[a] Includes oral iron and all formulations of IV iron other than Injectafer

Other adverse reactions reported by ≥0.5% of treated patients include abdominal pain, diarrhea, gamma glutamyl transferase increased, injection site pain/irritation, rash, paraesthesia, sneezing. Transient decreases in laboratory blood phosphorus levels (<2 mg/dL) have been observed in 27% (440/1638) of patients in clinical trials.

6.2 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.

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 (rarely reported event)
- Nervous system disorders: Syncope
- Respiratory, thoracic and mediastinal disorders: Dyspnea
- Skin and subcutaneous tissue disorders: Angioedema, erythema, pruritus, urticaria

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Published studies on the use of ferric carboxymaltose in pregnant women have not reported an association with ferric carboxymaltose and adverse developmental outcomes. However, these studies cannot establish or exclude the absence of any drug-related risk during pregnancy because the studies were not designed to assess for the risk of major birth defects (*see Data*). There are risks to the mother and fetus associated with untreated iron deficiency anemia in pregnancy (*see Clinical Considerations*).

In animal reproduction studies, administration of ferric carboxymaltose to rabbits during the period of organogenesis caused adverse developmental outcomes including fetal malformations and increased implantation loss at maternally toxic doses of approximately 12% to 23% of the human weekly dose of 750 mg (based on body surface area).

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically-recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations
Disease-Associated Maternal and/or Embryo/Fetal Risk
Untreated iron deficiency anemia in pregnancy is associated with adverse maternal outcomes such as post-partum anemia. Adverse pregnancy outcomes associated with iron deficiency anemia include increased risk for preterm delivery and low birth weight.

Data
Human Data
Published data from randomized controlled studies, prospective observational studies and retrospective studies on the use of ferric carboxymaltose in pregnant women have not reported an association with ferric carboxymaltose and adverse developmental outcomes. However, these studies cannot establish or exclude the absence of any drug-related risk during pregnancy because of methodological limitations, including that the studies were not primarily designed to capture safety data nor designed to assess the risk of major birth defects. Maternal adverse events reported in these studies are similar to those reported during clinical trials in adult males and non-pregnant females *[see Adverse Reactions (6.1)]*.

Animal Data
Administration of ferric carboxymaltose to rats as an one-hour intravenous infusion up to 30 mg/kg/day iron on gestation days 6 to 17 did not result in adverse embryonic or fetal findings. This daily dose in rats is approximately 40% of the human weekly dose of 750 mg based on body surface area. In rabbits, ferric carboxymaltose was administered as a one-hour infusion on gestation days 6 to 19 at iron doses of 4.5, 9, 13.5, and 18 mg/kg/day. Malformations were seen starting at the daily dose of 9 mg/kg (23% of the human weekly dose of 750 mg). Spontaneous abortions occurred starting at the daily iron dose of 4.5 mg/kg (12% of the human weekly dose based on body surface area). Pre-implantation loss was at the highest dose. Adverse embryonic or fetal effects were observed in the presence of maternal toxicity.

A pre- and post-natal development study was conducted in rats at intravenous doses up to 18 mg/kg/day of iron (approximately 23% of the weekly human dose of 750 mg on a body surface area basis). There were no adverse effects on survival of offspring, their behavior, sexual maturation or reproductive parameters.

8.2 Lactation
Risk Summary
The available published data on the use of ferric carboxymaltose in lactating women demonstrate that iron is present in breast milk. However, the data do not inform the full potential exposure of iron for the breastfed infant. Among the breastfed infants, there were no adverse events reported that were considered related to ferric carboxymaltose exposure through breastmilk. There is no information on the effects of ferric carboxymaltose on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Injectafer in addition to any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

Clinical Considerations
Monitor breastfed infants for gastrointestinal toxicity (constipation, diarrhea).

8.4 Pediatric Use
Safety and effectiveness have not been established in pediatric patients.

8.5 Geriatric Use
Of the 1775 subjects in clinical studies of Injectafer, 50% were 65 years and over, while 25% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

10 OVERDOSAGE

Excessive dosages of Injectafer may lead to accumulation of iron in storage sites potentially leading to hemosiderosis. A patient who received Injectafer 18,000 mg over 6 months developed hemosiderosis with multiple joint disorder, walking disability, and asthenia. Hypophosphatemic osteomalacia was reported in a patient who received Injectafer 4000 mg over 4 months. Partial recovery followed discontinuation of Injectafer.

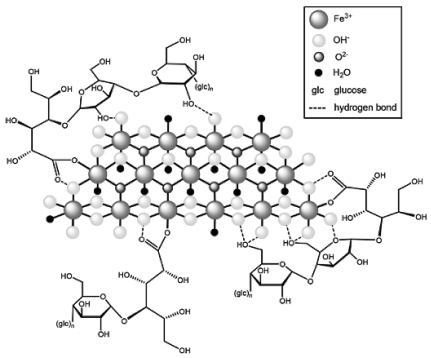
11 DESCRIPTION

Ferric carboxymaltose, an iron replacement product, is an iron carbohydrate complex with the chemical name of polynuclear iron (III) hydroxide 4(R)-(poly-(1→4)-*O*-α-D-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate. It has a relative molecular weight of approximately 150,000 Da corresponding to the following empirical formula:

$[FeO_x(OH)_y(H_2O)_z]_n\ [\{(C_6H_{10}O_5)_m\ (C_6H_{12}O_7)\}_l]_k$,

where $n \approx 10^3$, $m \approx 8$, $l \approx 11$, and $k \approx 4$
(*l* represents the mean branching degree of the ligand).

The chemical structure is presented below:



Injectafer (ferric carboxymaltose injection) is a dark brown, sterile, aqueous, isotonic colloidal solution for intravenous injection. Each mL contains 50 mg iron as ferric carboxymaltose in water for injection. Injectafer is available in 15 mL single-dose vials. Sodium hydroxide and/or hydrochloric acid may have been added to adjust the pH to 5.0-7.0.

Vial closure is not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ferric carboxymaltose is a colloidal iron (III) hydroxide in complex with carboxymaltose, a carbohydrate polymer that releases iron.

12.2 Pharmacodynamics

Using positron emission tomography (PET) it was demonstrated that red cell uptake of ^{59}Fe and ^{52}Fe from Injectafer ranged from 61% to 99%. In patients with iron deficiency, red cell uptake of radio-labeled iron ranged from 91% to 99% at 24 days after Injectafer dose. In patients with renal anemia, red cell uptake of radio-labeled iron ranged from 61% to 84% at 24 days after Injectafer dose.

12.3 Pharmacokinetics

After administration of a single dose of Injectafer of 100 to 1000 mg of iron in iron deficient patients, maximum iron concentration of 37 µg/mL to 333 µg/mL were obtained respectively after 15 minutes to 1.21 hours post dose. The volume of distribution was estimated to be 3 L.

The iron injected or infused was rapidly cleared from the plasma, the terminal half-life ranged from 7 to 12 hours. Renal elimination of iron was negligible.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with ferric carboxymaltose.

Ferric carboxymaltose was not genotoxic in the following genetic toxicology studies: *in vitro* microbial mutagenesis (Ames) assay, *in vitro* chromosome aberration test in human lymphocytes, *in vitro* mammalian cell mutation assay in mouse lymphoma L5178Y/TK+/- cells, *in vivo* mouse micronucleus test at single intravenous doses up to 500 mg/kg.

In a combined male and female fertility study, ferric carboxymaltose was administered intravenously over one hour to male and female rats at iron doses of up to 30 mg/kg. Animals were dosed 3 times per week (on Days 0, 3, and 7). There was no effect on mating function, fertility or early embryonic development. The dose of 30 mg/kg in animals is approximately 40% of the human dose of 750 mg based on body surface area.

14 CLINICAL STUDIES

14.1 Trial 1: Iron Deficiency Anemia in Patients Who Are Intolerant to Oral Iron or Have Had Unsatisfactory Response to Oral Iron

The safety and efficacy of Injectafer for treatment of iron deficiency anemia were evaluated in two randomized, open-label, controlled clinical trials (Trial 1 and Trial 2). In these two trials, Injectafer was administered at a dose of 15 mg/kg 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.

Trial 1: A Multi-center, Randomized, Active Controlled Study to Investigate the Efficacy and Safety of Intravenous Ferric Carboxymaltose (FCM) in Patients with Iron Deficiency Anemia (IDA), (NCT00982007) was a randomized, open-label, controlled clinical study in patients with iron deficiency anemia who had an unsatisfactory response to oral iron (Cohort 1) or who were intolerant to oral iron (Cohort 2) during the 14-day oral iron run-in period. Inclusion criteria prior to randomization included hemoglobin (Hb) <12 g/dL, ferritin ≤ 100 ng/mL or ferritin ≤ 300 ng/mL when transferrin saturation (TSAT) ≤ 30%. Cohort 1 subjects were randomized to Injectafer or oral iron for 14 more days. Cohort 2 subjects were randomized to Injectafer or another IV iron per standard of care [90% of subjects received iron sucrose]. The mean age of study patients was 43 years (range, 18 to 94); 94% were female; 42% were Caucasian, 32% were African American, 24% were Hispanic, and 2% were other races. The primary etiologies of iron deficiency anemia were heavy uterine bleeding (47%) and gastrointestinal disorders (17%).

Table 2 shows the baseline and the change in hemoglobin from baseline to highest value between baseline and Day 35 or time of intervention.

Table 2. Mean Change in Hemoglobin From Baseline to the Highest Value Between Day 35 or Time of Intervention (Modified Intent-to-Treat Population)

Hemoglobin (g/dL) Mean (SD)	Cohort 1		Cohort 2	
	Injectafer (N=244)	Oral Iron (N=251)	Injectafer (N=245)	IV SC[a] (N=237)
Baseline	10.6 (1.0)	10.6 (1.0)	9.1 (1.6)	9.0 (1.5)
Highest Value	12.2 (1.1)	11.4 (1.2)	12.0 (1.2)	11.2 (1.3)
Change (from baseline to highest value)	1.6 (1.2)	0.8 (0.8)	2.9 (1.6)	2.2 (1.3)
p-value	0.001		0.001	

SD=standard deviation; [a]: Intravenous iron per standard of care

Increases from baseline in mean ferritin (264.2 ± 224.2 ng/mL in Cohort 1 and 218.2 ± 211.4 ng/mL in Cohort 2), and transferrin saturation (13 ± 16% in Cohort 1 and 20 ± 15% in Cohort 2) were observed at Day 35 in Injectafer-treated patients.

14.2 Trial 2: Iron Deficiency Anemia in Patients with Non-Dialysis Dependent Chronic Kidney Disease

Trial 2: REPAIR-IDA, Randomized Evaluation of efficacy and safety of Ferric carboxymaltose in Patients with iron deficiency Anemia and Impaired Renal function, (NCT00981045) was a randomized, open-label, controlled clinical study in patients with non-dialysis dependent chronic kidney disease. Inclusion criteria included hemoglobin (Hb) ≤ 11.5 g/dL, ferritin ≤ 100 ng/mL or ferritin ≤ 300 ng/mL when transferrin saturation (TSAT) ≤ 30%. Study patients were randomized to either Injectafer or Venofer. The mean age of study patients was 67 years (range, 19 to 101); 64% were female; 54% were Caucasian, 26% were African American, 18% Hispanics, and 2% were other races.

Table 3 shows the baseline and the change in hemoglobin from baseline to highest value between baseline and Day 56 or time of intervention.

Table 3. Mean Change in Hemoglobin From Baseline to the Highest Value Between Baseline and Day 56 or Time of Intervention (Modified Intent-to-Treat Population)

Hemoglobin (g/dL) Mean (SD)	Injectafer (N=1249)	Venofer (N=1244)
Baseline	10.3 (0.8)	10.3 (0.8)
Highest Value	11.4 (1.2)	11.3 (1.1)
Change (from baseline to highest value)	1.1 (1.0)	0.9 (0.92)
Treatment Difference (95% CI)	0.21 (0.13, 0.28)	

Increases from baseline in mean ferritin (734.7 ± 337.8 ng/mL), and transferrin saturation (30 ± 17%) were observed prior to Day 56 in Injectafer-treated patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

NDC 0517-0650-01	750 mg iron/15 mL Single-Dose Vial	Individually boxed
NDC 0517-0650-02	750 mg iron/15 mL Single-Dose Vial	Packages of 2

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [See the USP controlled room temperature]. Do not freeze.

17 PATIENT COUNSELING INFORMATION

Prior History of Reactions to Parenteral Iron Products

Question patients regarding any prior history of reactions to parenteral iron products [*see Warnings and Precautions (5.1)*].

Serious Hypersensitivity Reactions

Advise patients to report any signs and symptoms of hypersensitivity that may develop during and following Injectafer administration, such as rash, itching, dizziness, lightheadedness, swelling and breathing problems [*see Warnings and Precautions (5.1)*].

Injectafer is manufactured under license from Vifor (International) Inc, Switzerland.

AMERICAN REGENT, INC.
SHIRLEY, NY 11967

IN0650
RQ1052-A

Patient Information

INJECTAFER (in-jekt-a-fer)

(ferric carboxymaltose injection)

What is INJECTAFER?

INJECTAFER is a prescription iron replacement medicine used to treat iron deficiency anemia in adults who have:

- intolerance to oral iron or who have not responded well to treatment with oral iron, **or**
- non-dialysis dependent chronic kidney disease

It is not known if INJECTAFER is safe and effective for use in children.

Who should not receive INJECTAFER?

Do not receive INJECTAFER if you are allergic to ferric carboxymaltose or any of the ingredients in INJECTAFER. See the end of this leaflet for a complete list of ingredients in INJECTAFER.

Before receiving INJECTAFER, tell your healthcare provider about all of your medical conditions, including if you:

- have had an allergic reaction to iron given into your vein
- have high blood pressure
- are pregnant or plan to become pregnant. It is not known if INJECTAFER will harm your unborn baby.
- are breastfeeding or plan to breastfeed. INJECTAFER passes into your breast milk. It is unknown whether INJECTAFER would pose a risk to your baby. Talk to your healthcare provider about the best way to feed your baby during treatment with INJECTAFER.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive INJECTAFER?

INJECTAFER is given intravenously (into your vein) by your healthcare provider in 2 doses at least 7 days apart.

What are the possible side effects of INJECTAFER?

INJECTAFER may cause serious side effects, including:

- **Allergic (hypersensitivity) reactions.** Serious life-threatening allergic reactions have happened in people who receive INJECTAFER. Other serious reactions including itching, hives, wheezing, and low blood pressure also have happened during treatment with INJECTAFER. Tell your healthcare provider if you have ever had any unusual or allergic reaction to any iron given by vein.
- **High blood pressure (hypertension).** High blood pressure, sometimes with face flushing, dizziness, or nausea, has happened during treatment with INJECTAFER. Your healthcare provider will check your blood pressure and check for any signs and symptoms of high blood pressure after you receive INJECTAFER.

The most common side effects of INJECTAFER include:

- nausea
- flushing
- dizziness
- high blood pressure
- low levels of phosphorous in your blood

These are not all the possible side effects of INJECTAFER.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about INJECTAFER

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about INJECTAFER that is written for health professionals.

What are the ingredients in INJECTAFER?

Active ingredient: ferric carboxymaltose

Inactive ingredients: water for injection. Sodium hydroxide and/or hydrochloric acid may have been added to adjust pH to 5.0-7.0.

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For more information go to www.injectafer.com or call 1-800-734-9236.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 02/2020