

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203565Orig1s000

LABELING

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: 20XX

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;
- who have non-dialysis dependent chronic kidney disease.

DOSAGE AND ADMINISTRATION

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

For patients weighing less than 50kg (110lb): 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

750 mg iron / 15 mL single-use vial(3)

FULL PRESCRIBING INFORMATION: CONTENTS*

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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)
- **Hypertension:** Monitor patients closely for signs and symptoms of hypertension following each Injectafer administration. (5.2)

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

- Nursing Mothers: Exercise caution when administered to a nursing woman. (8.3)

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

Revised: July 2013

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* 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;
- who have non-dialysis dependent chronic kidney disease.

2 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 not to exceed 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. Give each dose as 15 mg/kg body weight for a total cumulative dose not to exceed 1500 mg of iron per course.

The dosage of Injectafer is expressed in mg of elemental iron. Each mL of Injectafer contains 50 mg of elemental iron. Injectafer treatment may be repeated if iron deficiency anemia reoccurs.

Administer Injectafer intravenously, either as an undiluted slow intravenous push or by infusion. When administering as a slow intravenous push, give at the rate of approximately 100 mg (2 mL) per minute. 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 use only. Any unused drug remaining after injection must be discarded.

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.

3 DOSAGE FORMS AND STRENGTHS

750 mg iron / 15 mL single-use vial

4 CONTRAINDICATIONS

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 and 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 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)*].

5.3 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 adverse reactions are discussed in greater detail in other sections of the labeling:

- . Hypersensitivity Reactions [see *Warnings and Precautions (5.1)*]
- . Hypertension [see *Warnings and Precautions (5.2)*]
- . Lab test alterations [see *Warnings and Precautions (5.3)*]

6.1 Adverse Reactions in Clinical Trials

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 $\geq 1\%$ of treated patients are shown in the following table.

Table 1. Adverse reactions reported in $\geq 1\%$ 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 $\geq 0.5\%$ 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) patients in clinical trials.

6.2 Post-marketing Experience

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 serious adverse reactions have been most commonly reported from the post-marketing spontaneous reports with Injectafer: urticaria, dyspnea, pruritis, tachycardia, erythema, pyrexia, chest discomfort, chills, angioedema, back pain, arthralgia, and syncope. One case of hypophosphatemic osteomalacia was reported in a

subject who received 500 mg of Injectafer every 2 weeks for a total of 16 weeks. Partial recovery followed discontinuation of Injectafer.

7 DRUG INTERACTIONS

Formal drug interaction studies have not been performed with Injectafer .

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

Adequate and well controlled studies in pregnant women have not been conducted. However, animal reproduction studies have been conducted with ferric carboxymaltose. In these studies, administration of ferric carboxymaltose to rabbits during the period of organogenesis caused 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 incidence of major malformations in human pregnancies has not been established for Injectafer. However, all pregnancies, regardless of exposure to any drug, has a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. Injectafer should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

Administration of ferric carboxymaltose to rats as a one-hour intravenous infusion up to 30 mg/kg/day iron on gestation days 6 to 17 did not result in adverse embryofetal 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 embryofetal 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.

8.3 Nursing Mothers

A study to determine iron concentrations in breast milk after administration of Injectafer (n=11) or oral ferrous sulfate (n=14) was conducted in 25 lactating women with postpartum iron deficiency anemia. Mean breast milk iron levels were higher in lactating women receiving Injectafer than in lactating women receiving oral ferrous sulfate.

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. [see *Post-marketing Experience (6.3)*].

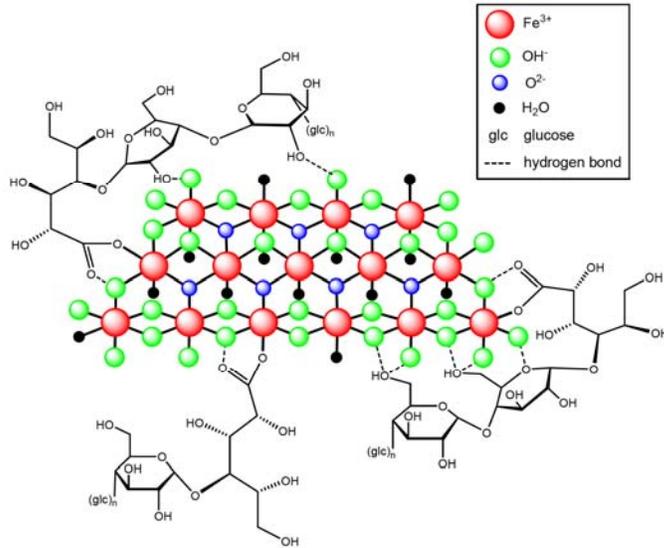
11 DESCRIPTION

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:



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-use 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% after 24 days 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 levels of 37 $\mu\text{g/mL}$ to 333 $\mu\text{g/mL}$ 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

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.

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

Trial 1 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 \leq 100 ng/mL or ferritin \leq 300 ng/mL when transferrin saturation (TSAT) \leq 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) 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 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 96); 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 at Day 56 in Injectafer-treated patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

NDC 0517-0650-01 750 mg iron/15 mL Single-Use Vial Individually boxed
 NDC 0517-0650-02 750 mg iron/15 mL Single-Use 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

- Question patients regarding any prior history of reactions to parenteral iron products.
- Advise patients of the risks associated with Injectafer.
- 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)*]

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

AMERICAN
REGENT, INC.
SHIRLEY, NY 11967

IN0602
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Patient Information

INJECTAFER (ferric carboxymaltose injection)

Please read this information carefully before taking this medication. This summary does not tell you everything about INJECTAFER. Speak with your doctor or healthcare professional if there is something you do not understand or if you would like to learn more about INJECTAFER. Your doctor or healthcare professional is your best source of information about this medicine.

What is INJECTAFER?

Iron is a mineral that the body needs to produce red blood cells. When the body does not get enough iron, it cannot produce the number of normal red blood cells needed to keep you in good health. This condition is called iron deficiency (iron shortage) or iron deficiency anemia.

INJECTAFER is used to treat iron deficiency anemia. Iron deficiency anemia may be caused by several medical conditions including heavy menstrual bleeding, pregnancy, childbirth, inflammatory bowel disease, other malabsorption diseases, bariatric surgery, or chronic kidney disease.

General information about using INJECTAFER safely and effectively

Injectable iron is administered only by or under the supervision of your health care professional.

Serious or life threatening allergic reactions have been reported with intravenous iron products. Tell your health care professional if you have ever had any unusual or allergic reaction to any IV iron.

Patients should report to their healthcare professional any signs and symptoms of an allergic reaction to INJECTAFER, in particular rashes, shortness of breath and wheezing.

Iron is not easily eliminated from the body, and its build up may lead to a condition called iron overload which may be harmful. Certain medical conditions such as liver disease may also make you more likely to develop iron overload. Ask your doctor or healthcare professional.

Who should not take INJECTAFER?

You should not be given INJECTAFER if you have anemia that is not caused by iron deficiency, or if you have iron overload.

If you are pregnant or plan to become pregnant please notify your doctor or healthcare professional. They will decide whether it is safe for you to receive INJECTAFER.

How should I take INJECTAFER?

INJECTAFER is administered intravenously (into your vein) by your doctor or health care professional in two doses.

What should I avoid while taking INJECTAFER?

You should not take iron supplements by mouth if you are receiving iron injections. Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements.

What are the possible side effects of INJECTAFER?

The side effects of INJECTAFER are infrequent, usually mild and generally do not cause patients to stop treatment. The most common side effects are nausea, injection site reactions (including pain or bruising at the injection site), asymptomatic reductions in blood phosphorus, flushing, headache, hypertension, dizziness, and increased alanine aminotransferase. Potentially long lasting brown staining of skin near injection site may occur.

These are not all the possible side effects of INJECTAFER. For more information ask your doctor or healthcare professional.

Talk to your doctor if you think you have side effects from taking INJECTAFER.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EDVARDAS KAMINSKAS
07/25/2013