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.

DOSE 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)

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

FULL PRESCRIBING INFORMATION: CONTENTS*
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
2.2 Preparation and Administration
2.3 Repeat Treatment Monitoring Safety Assessment
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity Reactions
5.2 Symptomatic Hypophosphatemia
5.3 Hypertension
5.4 Laboratory Test Alterations
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Post-marketing Experience
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation

8.4 Pediatric Use
8.5 Geriatric Use
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
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
14.2 Trial 2: Iron Deficiency Anemia in Patients with Non-Dialysis Dependent Chronic Kidney Disease
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION
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 inactive components. (4)

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% (67/1775) 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 [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 1,500 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

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

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, glucose intolerance, nausea, rash, paraesthesia, sneezing, transient decreases in laboratory blood phosphate 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 on gestation days 6 to 17 did not result in adverse embryonic or fetal outcomes. 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 (25% 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.
Injectafer is manufactured under license from Vifor (International) Inc, Switzerland.

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

18 PATIENT COUNSELING INFORMATION

Injectafer is not made with natural rubber latex.

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 observed at Day 35 in Injectafer-treated patients.

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.

15 EFFICACY AND SAFETY OF INTRAVENOUS FERRIC CARBOXYMALTOSE (FCM) IN PATIENTS WITH IRON DEFICIENCY ANEMIA AND IMPAIRED RENAL FUNCTION

Table 1 shows the baseline and the change in hemoglobin from baseline to highest value between baseline and Day 35 or time of intervention (Modified Intent-to-Treat Population).

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)].

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For information about Injectafer, please see Instructions for Use.

American Regent, Inc.
Shirley, NY 11967

INO650
RO1052-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
• dizziness
• low levels of phosphorous in your blood
• flushing
• high blood pressure

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.

AMERICAN REGENT, INC.
SHIRLEY, NY 11967

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