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Current Considerations for Recognizing and Treating Iron Deficiency Anemia in Women

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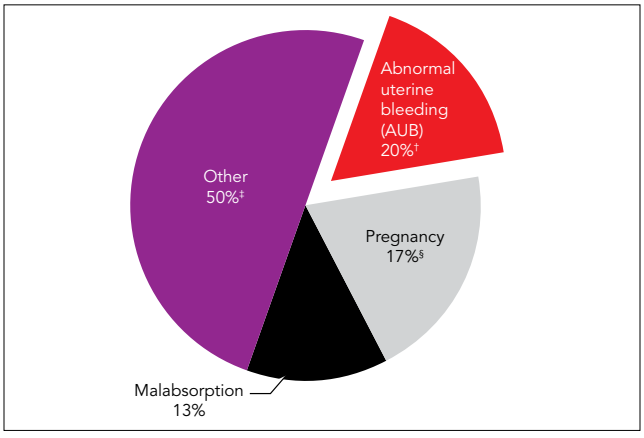
Iron deficiency anemia (IDA) is one of the most common causes of anemia in women, and is the most common cause of anemia in the majority of the world outside of Europe and North America, according to a prevalence regional ranking from 2010.[1] IDA affects women across the lifespan, including during menstruation, pregnancy, and the postpartum period.§[2] In the United States, IDA affects 1 in 5 women of childbearing age.[3] Additionally, some ethnic subgroups may be particularly vulnerable to IDA. These include African American and Mexican American women.[4] Recurrent blood loss is a common cause of IDA, particularly from abnormal uterine bleeding (AUB) which is characterized by abnormally heavy and abnormal timing of menstrual bleeding.[2,5,6] AUB may be present in 14% to 25% of reproductive-aged women.[5] The most common causes of IDA among women who received intravenous (IV) iron treatment from April 2018 through June 2018, as reported by referring or infusing OB/GYNs are presented in **FIGURE 1**.[7]

FIGURE 1 Underlying conditions in women receiving intravenous iron supplementation who were infused or referred by OB/GYNs*[7]



*Data based on Projected IMS Medical (Dx) Claims (January 2017-December 2017) of 12,885 patients infused or referred by OB/GYNs.

†Abnormal uterine bleeding (AUB) previously was referred to as heavy uterine bleeding (HUB).

‡Includes claims submitted with diagnosis codes not listed in any other category (left blank). Category also includes claims for underlying conditions such as cancer and gastric bypass, among others.

§Injectafer has not been studied in pregnant women. Injectafer should be prescribed during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Identifying IDA in women

Sufficient stores of iron are necessary for critical processes in the body including oxygen transport and energy metabolism.[8] Common symptoms of IDA may include headache, chest pain, pale or yellow skin, fatigue, and shortness of breath.[9] Because symptoms can be variable and nonspecific, they frequently are unreported or may be accepted as normal by women. Physicians should consider IDA as part of a differential diagnosis if patients report nonspecific symptoms such as fatigue. Once symptoms are present, testing can proceed as outlined below. There is no consensus in the United States on recommendations for IDA screening in asymptomatic women. Practices may consider more periodic screening and management protocols in women who have AUB or are at risk for IDA.

Due to the prevalence and burden of symptom persistence and progression when IDA goes undiagnosed, all adult women of reproductive age should be screened periodically. Additionally, assessments of IDA risk can be easily used as part of the routine monitoring of gynecologic patients. In a survey of 503 fellows and junior fellows, women's health specialists reported inconsistent IDA screening and symptom-directed practices, with approximately 25% reporting regular IDA screening in nonpregnant or postpartum patients, and 40% to 43% screening for IDA based on risk factors.[10] Laboratory markers are central to proper evaluation of healthy iron levels.[9] When ordering a complete blood count (CBC), the main tests to consider for IDA are hemoglobin, transferrin saturation (TSAT), and serum ferritin. Specialists may order iron or other tests; however, for routine screening, review of hemoglobin, TSAT, and serum ferritin levels is the first step to determine

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TABLE Laboratory tests for iron deficiency anemia[11–13]

Laboratory test	Normal range in nonpregnant women[11]	IDA in nonpregnant women[11]
Hemoglobin	>12 g/dL	<12 g/dL
TSAT	20%–50%	<20%
Serum ferritin	20–200 µg/mL	<10–15 µg/mL[11,13]
Hematocrit	36%–48%[12]	<36%
MCV	80–95 fL	<80 fL
Serum Iron	60–170 mcg/dL	<60 mcg/dL

Normal laboratory values may vary based on patient characteristics/comorbidities and by laboratory.
Abbreviations: IDA, iron deficiency anemia; MCV, mean corpuscular volume; TSAT, transferrin saturation.

whether further action is appropriate (**TABLE**).[11-13] Serum ferritin becomes elevated in the presence of inflammation, making TSAT a more reliable marker in these patients.[14]

Thus, common conditions, such as AUB, that women's health care providers see on a daily basis should trigger the start of an IDA workup. Given what has been covered so far, let's think about the following type of patient:

Vanessa
24-year-old G_0 female

Case Presentation
- Reports heavy menstrual bleeding, including bleeding through her tampons and pads
- Reports periods lasting twice as long as previous periods and coming every 30 to 35 days instead of every 25 since last visit
- Denies abdominal pain, shortness of breath, or lightheadedness

Considerations
- Medical history unremarkable
- Vital signs: 5'6", 155 lb
- Temp 98.4, HR 80, BP 125/86

Do you order any tests?

If so, which ones and what are you looking for?

Testing recommendations
The doctor considers ordering a CBC and an iron panel for Vanessa's abnormal uterine bleeding including TSH, prolactin, workup for polycystic ovarary syndrome, and transvaginal ultrasonography.

We'll return to this case at the end of the article.

Abbreviations: BP, blood pressure; CBC, complete blood count; HR, heart rate; TSH, thyroid-stimulating hormone.
Note: Patient described is fictional and for illustrative purposes only.

Treating IDA

Oral iron supplementation

First-line treatment of IDA in most patients is oral iron supplementation; however, it is estimated that less than 10% of oral iron is generally absorbed.[15] Additionally, interactions with other medications and dietary restrictions must be considered to optimize absorption. Patient tolerance of side effects also plays a critical role in the effectiveness of first-line oral iron therapy. Common side effects, including nausea, vomiting, constipation, diarrhea, stomach pain, and leg cramps, have been reported in 10% to 40% of patients taking oral iron, which could necessitate reduction of dose or dosing frequency.[16,17] Adherence rates for oral therapy have been reported to range from 40% to 60%.[18]

After initiation of treatment, it is important to monitor the patient's response with the appropriate laboratory tests; however, there are no universally accepted standards, timing, or thresholds for monitoring IDA during treatment. Hemoglobin is a critical marker of IDA treatment response.[19] Hemoglobin should increase over the first several weeks of treatment, with the deficit halved by about 4 weeks, and return to normal levels in 6 to 8 weeks.[20]

Intravenous iron treatment for patients intolerant or unresponsive to oral iron therapy

IV iron may be an option when iron levels have not achieved repletion in patients taking oral therapy, whether due to side effects or malabsorption. IV iron treatment ensures that 100% of the iron is delivered into the patient's bloodstream to be utilized in hemoglobin production or stored as ferritin for future use. Several IV iron preparations are available in the United States, including ferric carboxymaltose, iron sucrose, sodium ferric gluconate, ferumoxytol, and iron dextran. Each treatment option may have a different indication, use, and safety profile. Please refer to the respective prescribing information for each product. Iron sucrose, iron dextran, and sodium ferric gluconate are established IV therapies that may require treatment courses in multiple doses over several weeks.[21] Iron dextran in particular is associated with the highest risk for anaphylactic reactions that have contributed to apprehension about all IV iron treatments.[22] Newer dextran-free IV iron formulations have been developed to allow larger doses to be given with fewer doses administered.[23]

Injectafer® (ferric carboxymaltose injection)

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 who have intolerance to or who have had unsatisfactory response to oral iron, or those with nondialysis-dependent chronic kidney disease.[23] It is the most studied IV iron with more than 40 clinical trials including no less than 8300 patients and has been approved in more than 75 countries with an excess of 7.5 million patient-years of postmarketing treatment experience worldwide.[24]

Ferric carboxymaltose can be administered via IV push over 7.5 minutes per dose or via a slow infusion protocol of at least 15 minutes per infusion.[23] 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.[23]

In a randomized, open-label, active-controlled multicenter trial including 1011 adults with IDA, ferric carboxymaltose was compared to oral iron in a cohort of patients who did not have an adequate response to oral iron during a 2-week run-in period (<1.0 g/dL increase in hemoglobin), and to standard-of-care IV iron in patients who were inappropriate* for or intolerant to oral iron therapy.[7] Ferric carboxymaltose clinical trials did not include pregnant patients. Ferric carboxymaltose 1500 mg demonstrated

*Patients inappropriate for oral iron therapy were not included in the indication for Injectafer®

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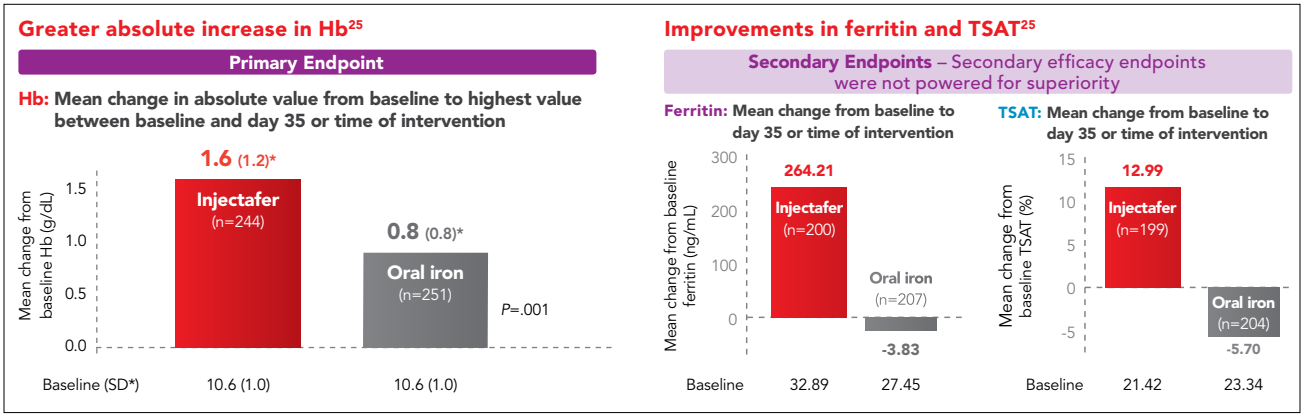
FIGURE 2 Ferric carboxymaltose 1500 mg provided greater improvements in measures of iron repletion than oral iron supplementation[25]



Abbreviations: Hb, hemoglobin; TSAT, transferrin saturation.
*Standard deviation.

significantly greater increases in hemoglobin than oral iron, as well as greater increases in ferritin and TSAT.[25] In secondary and post hoc analyses, ferric carboxymaltose 1500 mg also provided greater increases in hemoglobin than other IV iron in patients who were not candidates for oral iron therapy, including both absolute hemoglobin and the proportion of patients achieving a hemoglobin target of >12 g/dL (**FIGURE 2**).[25]

Safety Information

The most frequent adverse reactions reported in at least 2% of study patients in 2 pivotal clinical trials of ferric carboxymaltose were nausea, hypertension, flushing, hypophosphatemia, and dizziness.[23] In the treatment of pregnant and postpartum women, maternal adverse events reported were similar to those reported in adult males and nonpregnant females. Published studies on the use of ferric carboxymaltose in pregnant women have not shown an association with 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 to assess the risk for major birth defects.

Now let's follow up with our case presentation and think about the next steps for treatment and follow-up.

Vanessa

24-year-old G_0 female

Testing Treatment Order

- Hb: 9.3 g/dL
- TSAT: 11.6%
- Ferritin: 12 mcg/L
- Hct: 25%
- MCV: 78 fL
- TSH and prolactin normal
- Workup for oligo-ovulation c/w anovulation and TVUS normal

Diagnosis

- The clinical presentation and lab results are indicative of IDA
- The doctor has diagnosed Vanessa with IDA and starts her on a course of oral iron therapy

Treatment Prescription

- Trial of oral iron supplementation discontinued by patient after discussion with physician following intolerance to oral iron
- IV ferric carboxymaltose 1500 mg administered

Follow-up

- Patient is on medical management for anovulation and is using oral contraceptives to decrease frequency and length of menses
- Lab values 6 weeks post ferric carboxymaltose administration
  - Hb: 10.4 g/dL
  - TSAT: 20%
  - Ferritin: 193 mcg/L
  - Hct: 35%
  - MCV: 82 fL
- Follow-up every 6 months

Abbreviations: CBC, complete blood count; Hb, hemoglobin; Hct, hematocrit; IV, intravenous; MCV, mean corpuscular volume; TSAT, transferrin saturation; TSH, thyroid-stimulating hormone; TVUS, transvaginal ultrasound.

Case Discussion and Summary

This case highlights important elements of identifying and managing IDA in women. Additionally, the prevalence of IDA in women is high, particularly among postpartum women and those with AUB, although half of women with IDA have other or additional etiologies. Clinicians should be vigilant about following up with patients and considering the possibility of IDA in the presence of some or many classic symptoms, or none. IDA is diagnosed and monitored based on laboratory values, including timely follow-up to monitor progress to iron repletion. Finally, IV iron may be an option when iron levels have not achieved repletion in patients taking oral therapy, whether due to side effects or malabsorption. Only consistent follow-up and monitoring can determine if there is progress in resolving a patient's IDA.

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IMPORTANT SAFETY INFORMATION

INDICATIONS

Injectafer® (ferric carboxymaltose injection) is an iron replacement product 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, and in adult patients with 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

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 serious adverse reactions have been most commonly reported from the post-marketing spontaneous reports: urticaria, dyspnea, pruritus, tachycardia, erythema, pyrexia, chest discomfort, chills, angioedema, back pain, arthralgia, and syncope.

To report adverse events, please contact American Regent at 1-800-734-9236. You may also contact the FDA at www.fda.gov/medwatch or 1-800-FDA-1088.

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Please see pages S5-S8 for 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

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 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)
- **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

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

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

Revised: 04/2018

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;
- 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-dose 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

Injection: 750 mg iron / 15 mL single-dose 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, 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)]*
- Laboratory 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 ≥ 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) 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, pruritus, 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.

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 (IDA) 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 (IDA) in pregnancy is associated with adverse maternal outcomes such as post-partum anemia. Adverse pregnancy outcomes associated with IDA 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 a 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. [*see Adverse Reactions (6.2)*].

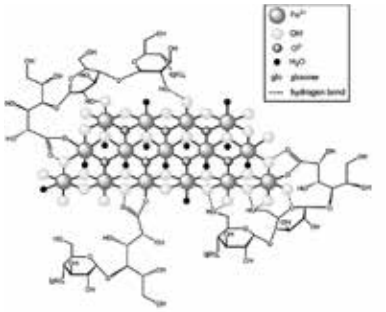
11 DESCRIPTION

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

- 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

IN0650
RQ1052-P

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
- 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: 04/2018