PEER perspectives

Issue 2 • July 2025 • ID in HF and IDA

INFUSING WITH CONFIDENCE:

ADDRESSING ID IN HF AND IDA THROUGH IV IRON THERAPY

INSIDE THIS ISSUE:

- Recognizing and diagnosing iron deficiency (ID) in heart failure (HF) and iron deficiency anemia (IDA) across patient populations
- The use of oral iron for ID in HF and IDA and how inflammation influences treatment efficacy
- Peer perspectives and best practices on how dextran-free IV irons can help address ID in HF and IDA
- How to navigate efficient patient referral with ID in HF and IDA to infusion centers

FEATURING INTERVIEW AND PEER PERSPECTIVES FROM:

Dr. Satheesh Kathula
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Peer perspectives come from Dr. Satheesh Kathula, who has been compensated by Daiichi Sankyo Inc.

How ID in HF and IDA Impact Patient Care Across Conditions

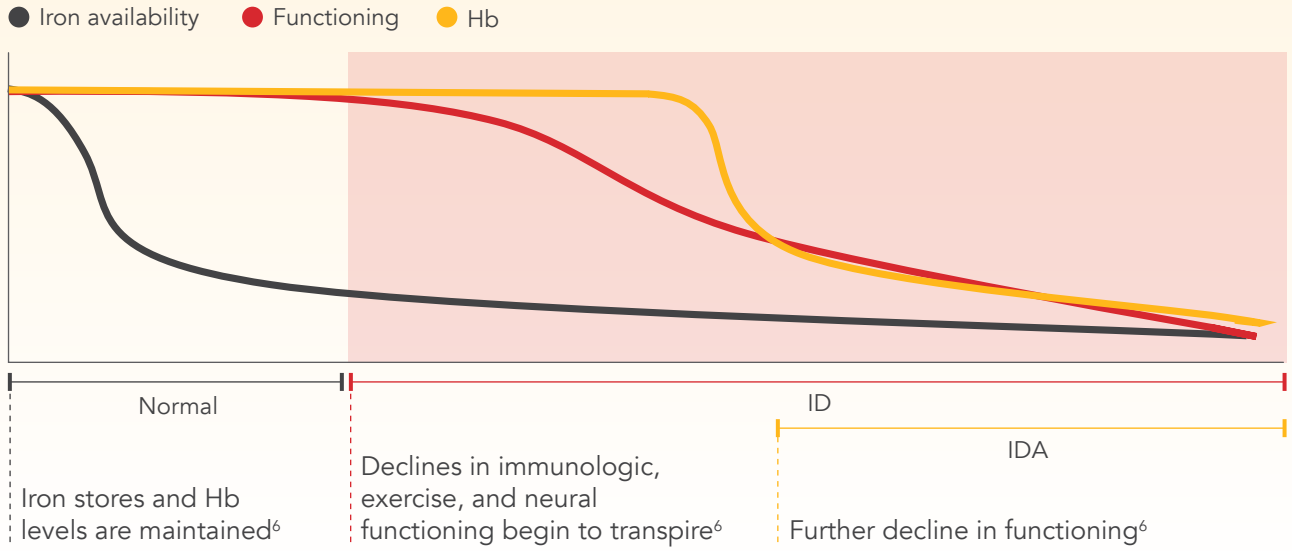
The causes of ID in HF and IDA primarily fall within 3 categories, which are blood loss, insufficient absorption, and inadequate intake. The manifestations are varied and may include heavy menstrual bleeding, bleeding ulcers, colon cancer, intestinal surgeries, Crohn's disease, or celiac disease. Inadequate nutritional intake due to eating disorders or a diet low in iron-rich foods can also lead to ID in HF or IDA.[1-4]

The Causes of ID in HF/IDA Fall Into 3 Categories:

Blood loss | Insufficient absorption | Inadequate intake

How ID in HF Impacts Functioning Before Anemia Develops

- Under normal conditions, iron stores and hemoglobin (Hb) levels are maintained, allowing for normal functioning[5]
- When ID in HF occurs, declines in immunologic, exercise, and neural functioning begin to transpire[6]
- Once iron stores fall below 100 mg (ferritin <10 ng/mL to 15 ng/mL) and transferrin saturation (TSAT) drops below 15%, IDA occurs, resulting in an even further decline in functioning[6]



A lot of people complain of fatigue, but sometimes we don't investigate other causes. Anemia can be one of them, and anemia can be due to several reasons. People who have near to normal Hb can also have ID and still require iron assessment.

– Dr. Satheesh Kathula, hematologist/oncologist

In the US, approximately **6.5 million** adults and over **850,000** pediatric patients have IDA.[7-9]
~6 million patients in the US have chronic HF[10]; **~50%** of all patients with HF **have ID.**[11]

ID in HF and IDA: Uncovering Key Populations Impacted

Cancer[12]

44%-50% of tumor types have IDA

- Anemia was detected in 50.4% of iron-deficient patients with solid tumors
- Anemia was detected in 43.7% of iron-deficient patients with hematologic malignancies
- 82% of iron-deficient patients had functional ID (across tumor types)

Gastrointestinal Conditions

*36%-76% of patients with inflammatory bowel disease (IBD) have IDA[13]**

- Most common cause of anemia in IBD[14]

Non-dialysis Dependent Chronic Kidney Disease (NDD-CKD)

*57.8%-58.8% of men and 69.9%-72.8% of women with NDD-CKD have low iron tests (National Health and Nutrition Examination Survey III)[15]**

- Higher prevalence of anemia with advanced disease[16]

HF

~50% of HF patients exhibit ID; 17% of patients with chronic HF have ID and anemia[17,18]

- Risk factors for ID in HF include female sex, advanced stages of HF, elevated N-terminal pro–B-type natriuretic peptide (NT-proBNP), chronic kidney disease (CKD), and C-reactive protein (CRP)[17,18]

Women[19†]

~20% (1 in 5) of childbearing-aged women in the United States have IDA

- Women are at greater risk for IDA due to blood loss during menstruation and high iron demands during pregnancy

Pediatric Patients

20.1% of 0–4-year-olds and 5.9% of 5–14-year-olds have IDA[20‡]

- Infants, preschool-aged children, and adolescents undergoing growth spurts are commonly impacted[21]

* Defined in reference as a serum ferritin <100 ng/mL or TSAT <20%. Authors concluded this remarkably high prevalence might indicate these indices may not be specific enough and may falsely identify too many patients as iron deficient.[15]

† Published studies and available data from postmarketing reports with IV Injectafer are insufficient to assess the risk for pregnant women of major birth defects and miscarriage.[22]

‡ In industrialized countries.[20]

A Closer Look at Diagnosing ID in HF & IDA

Common signs and symptoms of IDA may include[23]:

- Fatigue
- Weakness
- Dizziness
- Shortness of breath
- The signs and symptoms of IDA can overlap with those of other conditions[24-27]

Other signs and symptoms[23,28]:

- Headache
- Chest pain
- Pale skin
- Arrhythmia
- Lightheadedness
- Brittle nails
- Coldness in extremities
- Pica (craving nonfood items such as dirt or ice)

Early and accurate diagnosis of ID in HF and IDA is incredibly important. If your patients' Hb, ferritin, and TSAT values fall below normal levels, they may require iron supplementation.[29,30]

The American College of Cardiology (ACC)/ American Heart Association (AHA)/Heart Failure Society of America (HFSA) Guideline[1] states iron tests to diagnose ID in HF are a Class 1 recommendation[29]:

Class 1 – recommendation (strong), benefit >>> risk

Routine baseline assessment of all patients with HF should include iron studies

ID in HF is usually defined as ferritin level <100 ng/mL or 100 ng/mL to 300 ng/mL, if the TSAT is <20%

ID in HF and IDA can be diagnosed by testing for 3 key indices[30,31]:

Hb[32]:
- Hb production requires sufficient levels of stored iron and adequate TSAT

Ferritin[33]:
- When the body requires more iron than the diet provides, ferritin supplies a reservoir from which iron can be metabolized

TSAT[34]:
- Transferrin transports iron through the body so that it can be used to produce Hb. TSAT is decreased in chronic ID

NORMAL LEVELS IN HEALTHY ADULT PATIENTS*	
Hb[35]	**M:** 13.5 g/dL-17.5 g/dL **F:** 12.0 g/dL-15.5 g/dL
Ferritin[36]	**M:** 40 ng/mL-300 ng/mL **F:** 20 ng/mL-200 ng/mL
TSAT[37]	**M:** 20%-50%† **F:** 20%-50%†

*Normal lab values may vary based on patient characteristics/comorbidities and by laboratory.

†Injectafer is not indicated to treat patients with CKD who are on dialysis or patients with anemia of chronic disease. For adult patients with CKD and anemia, guidelines issued by National Kidney Foundation (NKF) recommend IV iron for patients with a TSAT ≤30% and ferritin ≤500 ng/mL. Consult the NKF guidelines for a complete list of recommendations for lab values when starting treatment.[22]

Sometimes the symptoms are so vague ...That's why we need to look at if TSAT is <20%. Some people don't realize that a TSAT level of 18-19% is considered out of normal range and patients will get sent back to me with a missed diagnosis of ID. As long as TSAT is <20%, you should treat it as if its ID or IDA.

– Dr. Satheesh Kathula, hematologist/oncologist

Understanding Inflammation: Its Impact on Iron Absorption

There are many different chronic conditions that can cause inflammation that may lead to anemia, including:

- Congestive heart failure (CHF)[38]
- Diabetes[39]
- Obesity[24]
- CKD[39]
- Autoimmune diseases, such as arthritis and lupus[39]
- Inflammatory bowel disease, such as Crohn's disease or ulcerative colitis[14]
- Cancer[38,39]

Hepcidin levels are significantly elevated in individuals with inflammation, causing ferroportin degradation, blocking oral iron absorption, as well as iron release from macrophages[40]

Chronic inflammation leads to a decrease in oral iron absorption and defective mobilization of iron stores[40]

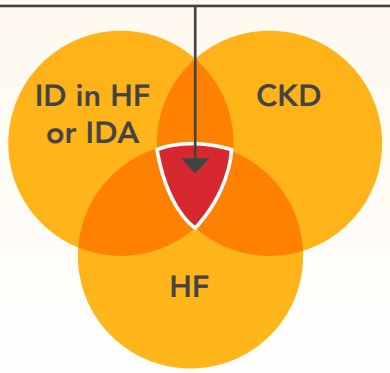
"First of all, oral iron is not so pleasant because it can cause a lot of side effects, like constipation, diarrhea, and nausea. Secondly, response may be slow; I try patients on oral iron for 3-4 weeks, and if the response is very slow, if the patient has more symptoms, or there is noncompliance ... I have a low threshold to switch to IV iron in these patients."

– Dr. Satheesh Kathula, hematologist/oncologist

Inflammatory conditions (such as CKD or HF) alter the body's iron sequestering methods.[41]

These conditions also modulate the relationship between iron stores and serologic markers, rendering conventional thresholds insensitive for detecting ID in HF and complicating clinical decision-making.[41]

The coexistence of CKD and HF with ID results in decreased exercise capacity.[42]



Using oral iron may have limited efficacy in those with inflammation from chronic anemia. IV iron should be considered for these patients.[38] Inflammation is a key component of both the CHF and CKD syndrome and is a key contributor to anemia in patients with ID in HF or IDA in comorbid NDD-CKD.[43]

Adherence issues

- Data show the adherence rate for oral iron is 40% to 60%[44]
- Adherence may be affected by side effects[45]

Side effects

- 10%-40% of patients taking oral iron may experience side effects, which may necessitate dose reduction or modification[46]

Absorption

Even in healthy patients, less than 10% of oral iron is absorbed.[3]

Per the American Gastroenterological Association Guidelines, a response (with improvements in Hb concentration) to oral iron supplementation is typically evident within 1 month of treatment. If a response is not seen, further assessments are needed.[47]

Consider testing your patients beginning 14-30 days after starting oral iron to see if they are having an adequate response[48,49]

REVIEWING INJECTAFER: A DEXTRAN-FREE* IV IRON

Injectafer has been studied in more than 8800 patients enrolled in more than 40 clinical trials, making it the most-studied IV iron therapy. Over 3 million patients in the US have been treated with Injectafer since its FDA approval in 2013.[7]

Injectafer is indicated for the treatment of IDA in[22]:

- Adults and pediatric patients 1 year of age and older who have either intolerance to oral iron or an unsatisfactory response to oral iron
- Adult patients who have non-dialysis-dependent chronic kidney disease

Injectafer is indicated for the treatment of ID in[22]:

- Adult patients with heart failure and New York Heart Association class II/III to improve exercise capacity

Injectafer is available as a 750 mg iron/15 mL single-dose vial and 100 mg iron/2 mL single-dose vial[22]

* Injectafer has a rate of serious anaphylactic/anaphylactoid reactions of 0.1% (2/1775). 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% (26/1,775) of these subjects.[22]

SELECTED SAFETY INFORMATION

CONTRAINDICATIONS

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

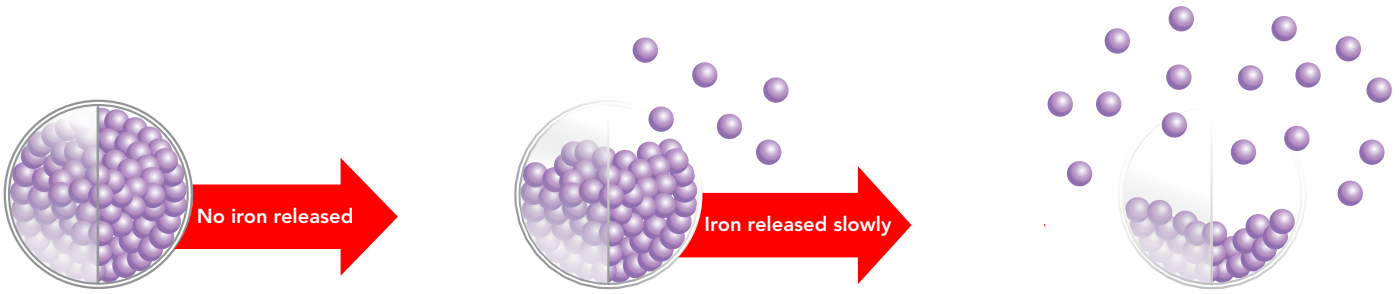
WARNINGS AND PRECAUTIONS

Symptomatic Hypophosphatemia

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

REVIEWING INJECTAFER: A DEXTRAN-FREE* IV IRON (CONT'D)

The structure of Injectafer controls the release of iron.[22,50]



After administration, enzymes in the blood partially degrade the Injectafer carbohydrate shell.[51]

Injectafer is then likely taken up by macrophages of the reticuloendothelial system, where enzymes continue breaking down the carbohydrate shell.[50,51]

This slow release of iron prevents the transferrin available for uptake from becoming fully saturated with iron.[52]

The number one thing patients with IDA find the most attractive about Injectafer is that it requires fewer doses. They only have to come twice, separated by a week, and then they might be done with infusions for 6 months or so. They love that they can go and live life and not sit in an infusion center, provided their Hb is normal. Patients have to come five times or eight times rather than coming two times? That's a no-brainer.

– Dr. Satheesh Kathula, hematologist/oncologist

On the following pages, learn more about the 4 Ds that differentiate Injectafer as a treatment option for IDA and ID in HF

DATA: Clinical trial data show Injectafer is an option for appropriate adult patients in both ID in HF and IDA in patients who are either intolerant or had an unsatisfactory response to oral iron and which has the only approval for ID in HF in the IV iron market[22,53-55]

DOSING: Injectafer may replenish your patients' iron deficit and provides the most iron per course of treatment—1500 mg (in two doses separated by at least 7 days)—in IDA and provides weight-based dosing and offers maintenance dosing beyond 6 weeks for patients with ID and HF[51,52]

DELIVERY: The only high dose IV iron that gives you options for administration[22,56-60]

DILUTION: Injectafer can be given up to 250 mL diluted for IV infusion or as an IV push[22]

SELECTED SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (CONT'D)

Symptomatic Hypophosphatemia (CONT'D)

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

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REVIEWING INJECTAFER: THE INFLUENCE OF THE 4 Ds

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Injectafer is the only dextran-free* IV iron that can offer:

- Approval for the treatment of ID in HF for appropriate adult patients[22]
- The sole high-dose IV iron indicated in pediatric patients with IDA in patients who are either intolerant or had an unsatisfactory response to oral iron[22]
- 2 options for administration (IV push or IV infusion)[22]
- Diluted administration option[22]
  - When administered via infusion, dilute up to 1000 mg of iron in no more than 250 mL of sterile 0.9% sodium chloride injection, United States Pharmacopeia (USP), and administer over at least 15 minutes
- Undiluted administration option[22]
  - When administering Injectafer 500 or 750 mg as a slow intravenous push, give at the rate of approximately 100 mg (2 mL) per minute. For Injectafer 1000 mg, administer as a slow intravenous push over 15 minutes

- Over 3 million patients in the US have been treated with Injectafer[7]
- Approved in 86 countries since initial European Union approval in 2007[7]
- Injectafer is the most-studied IV iron treatment, with more than 40 clinical trials and >8800 patients treated worldwide[7]
- Injectafer has more than 24 million patient-years in post-marketing treatment experience worldwide[7]

We have infusion centers with certain numbers of chairs, and there are a lot of patients that we need to take care of. Sometimes, we have to schedule patients 1 to 2 weeks in advance. Because we have a limited number of chairs, there are times where patient infusions get delayed. Every minute saved helps when trying to treat patients in an infusion center.

– Dr. Satheesh Kathula, hematologist/oncologist

* Injectafer has a rate of serious anaphylactic/anaphylactoid reactions of 0.1% (2/1775). 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% (26/1,775) of these subjects.[22]

SELECTED SAFETY INFORMATION

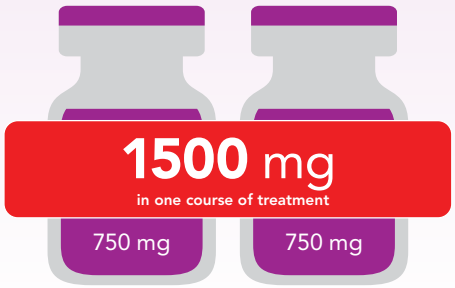
WARNINGS AND PRECAUTIONS (CONT'D)

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.

REVIEWING INJECTAFER: THE INFLUENCE OF THE 4 Ds (CONT'D)

Injectafer provides the most iron per course of treatment for IDA: up to 1500 mg in 2 doses of 750 mg separated by at least 7 days.[22,56-60]



1500 mg
in 1 course of treatment[22]

IV infusion over at least 15 minutes

In adults:

Slow IV push over 7.5 minutes

For patients weighing less than 50 kg (110 lb), the recommended dosage is Injectafer 15 mg/kg body weight intravenously in 2 doses separated by at least 7 days per course.[22]

Injectafer treatment may be repeated if IDA or ID in HF reoccurs.[22] Please see full prescribing information for HF dosing, administration, and pharmacy specifications.

- Over 90% of patients in pivotal trials received up to 1500 mg of total iron. Injectafer's 1500 mg dosing addresses average iron deficits, which are approximately 1500 mg. This average deficit was identified across 7 clinical trials that involved more than 4600 patients.[61] Clinical trial results showed that 1500 mg of iron resulted in a more rapid, robust Hb response, allowed more patients to reach target Hb levels, and required a longer mean time to retreatment with additional IV iron compared to 1000 mg of iron.[61]

> ***We give in two doses; 750 mg, one week apart (1500 mg total) and they're pretty much done in a week and don't need to come back to the infusion center. And when you're giving Injectafer in large doses like this, they'll have a faster response, too.***
> **– Dr. Satheesh Kathula, hematologist/oncologist**

SELECTED SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (CONT'D)

Hypersensitivity Reactions (CONT'D)

Only administer Injectafer when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions. In clinical trials, serious anaphylactic/anaphylactoid reactions were reported in 0.1% (2/1775) of subjects receiving Injectafer. Other serious or severe adverse reactions potentially associated with hypersensitivity which included, but were not limited to, pruritus, rash, urticaria, wheezing, or hypotension were reported in 1.5% (26/1775) of these subjects.

Hypertension

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

Laboratory Test Alterations

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

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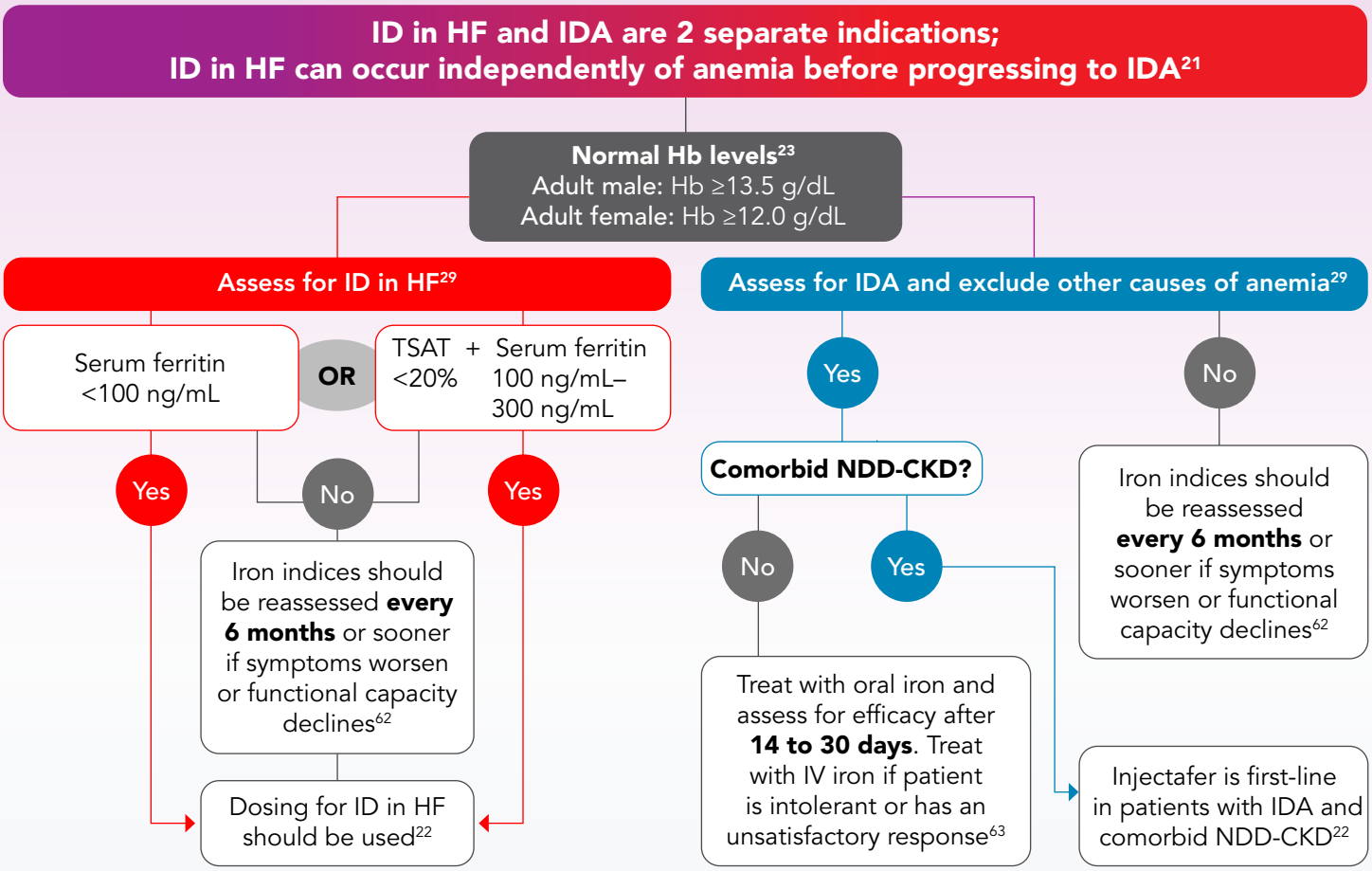
Click here to see Full Prescribing Information and see Important Safety Information on pages 18-19.

FROM DIAGNOSIS TO TREATMENT: BEST PRACTICES FOR MANAGING ID IN HF & IDA

Daiichi Sankyo, Inc. created the clinical algorithm tool to provide a clear and consistent approach to managing ID in HF and IDA in patients who are either intolerant or had an unsatisfactory response to oral iron and may help streamline variability in care, ensuring that healthcare professionals are more informed on evidence-based guidelines, leading to more predictable and reliable outcomes. The algorithm can also help disseminate up-to-date clinical knowledge to healthcare providers who may not specialize in ID in HF or IDA, possibly reducing the likelihood of omissions or incorrect steps in diagnosis or treatment. Finally, it can serve as an educational tool for new staff or trainees, promoting rapid acclimatization to clinical protocols.



It does affect the workflow. Definitely so. If you are bringing patients over and over, obviously that may take up more chair time and that may impact scheduling of other patients who need more time and consideration for their treatments, such as chemotherapy or immunotherapy.

– Dr. Satheesh Kathula, hematologist/oncologist

SELECTED SAFETY INFORMATION

ADVERSE REACTIONS

Adults

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

FROM DIAGNOSIS TO TREATMENT: BEST PRACTICES FOR MANAGING ID IN HF & IDA (CONT'D)

Of note, Injectafer is considered first-line treatment in appropriate adult patients with ID in HF[22]

ACC/AHA/HFSA Guideline states that IV iron is a Class 2a management for ID in patients with HF, regardless of anemia[29]

Therapy must be aimed at both the underlying condition and the treatment of IDA[64]

- Reduce or prevent continued iron loss[64]
- Restore Hb to normal levels[65,66]
- Replenish iron stores[65,66]

- Looking at serum ferritin and TSAT can help assess for ID. When the presence of ID is confirmed in a patient with HF, treatment with Injectafer should be initiated. Of note, Injectafer is considered first-line treatment in patients with HF and comorbid NDD-CKD who are diagnosed with IDA[22,29]
- In patients with IDA and comorbid NDD-CKD, treatment with Injectafer may be initiated. When the presence of IDA is confirmed in patients without NDD-CKD, treat with oral iron for 14 to 30 days. If the patient experiences intolerance or an unsatisfactory response, Injectafer may be administered[22,63]

"I find that often people don't test for iron because it doesn't cross their mind. Because I have been treating ID in HF and IDA for a long time ... I usually check for anemia and ID as a lot of primary care physicians don't know the intricacies of the indication. We test [as] frequently as we can for our patients."

– Dr. Satheesh Kathula, hematologist/oncologist

SELECTED SAFETY INFORMATION

ADVERSE REACTIONS (CONT'D)

Pediatric

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

Patients with Iron Deficiency and Heart Failure

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

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EXPLORING THE EFFICACY AND SAFETY OF INJECTAFER

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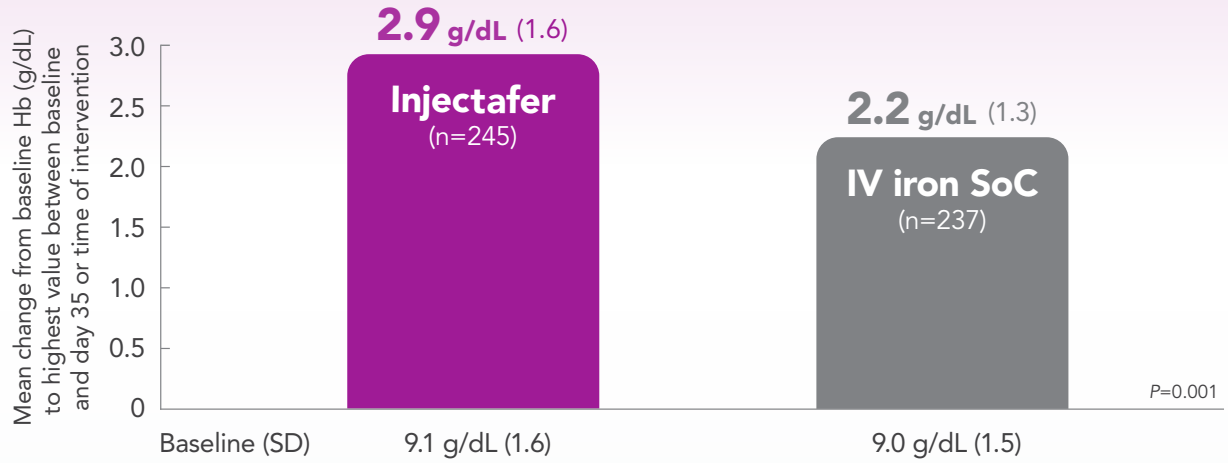
Pivotal trial 1: IDA in patients who are intolerant to oral iron or have had unsatisfactory response to oral iron

- Injectafer 1500 mg demonstrated significantly greater increases in Hb levels as compared with oral iron, regardless of the underlying etiology of IDA. No meaningful differences were observed in rates of death or major cardiovascular events between Injectafer and oral iron. Injectafer carries specific safety risks, including hypersensitivity and hypertension.[53]
- Injectafer provided significantly greater increases in Hb levels vs oral iron to day 35 in cohort 1[22,53]
- Injectafer showed greater improvements in Hb levels vs IV iron standard of care (SoC) to day 35 from baseline in cohort 2[53]

Hb: Mean change in absolute value from baseline to highest value between baseline and day 35 or time of intervention[22,53]



- In cohort 1, Injectafer resulted in significantly greater increases in Hb levels compared to oral iron on day 35 from baseline. Patients receiving Injectafer had a mean Hb increase of 1.6 from baseline, compared to 0.8 for those on oral iron. Additionally, 57% of patients on Injectafer achieved Hb levels >12 g/dL by day 35, versus 29% of those on oral iron[22,53]
- In Cohort 2 on day 35, Injectafer-treated patients showed numerically greater mean increases in hemoglobin (2.9 vs 2.2 g/dL) and iron indices (218.15 vs 74.65) compared to IV iron SoC. While 51% of Injectafer patients achieved Hb >12 g/dL versus 25% with IV iron SoC, these were secondary endpoints and the study was not powered to demonstrate statistical superiority.[53]

"You know, there is a good amount of Hb increase in Injectafer's clinical trials with general populations that have IDA and/or NDD-CKD. The pivotal trials make me feel comfortable because we see the Hb go up, as well as the ferritin and TSAT. Those are nice endpoints that the trial has and makes me feel secure using Injectafer in my patients."

– Dr. Satheesh Kathula, hematologist/oncologist

SELECTED SAFETY INFORMATION

ADVERSE REACTIONS (CONT'D)

Post-Marketing Experience

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

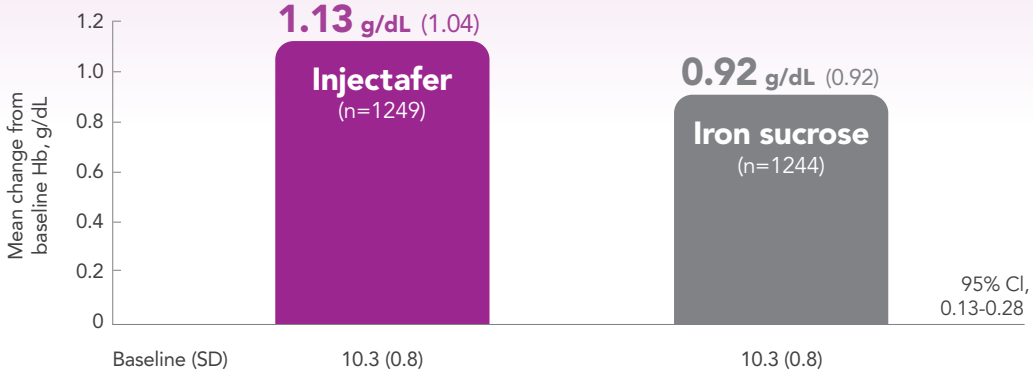
EXPLORING THE EFFICACY AND SAFETY OF INJECTAFER (CONT'D)

Pivotal trial 2: IDA in patients with NDD-CKD (REPAIR-IDA)

A higher percentage of subjects in the Injectafer group achieved an Hb increase of ≥1.0 g/dL by day 56 compared with the iron sucrose group (48.6% vs 41.0%; 95% CI, 3.6%–11.6%). There was no significant difference in the primary composite safety endpoint, including major adverse cardiac events such as death, myocardial infarction, or stroke.[22,53]

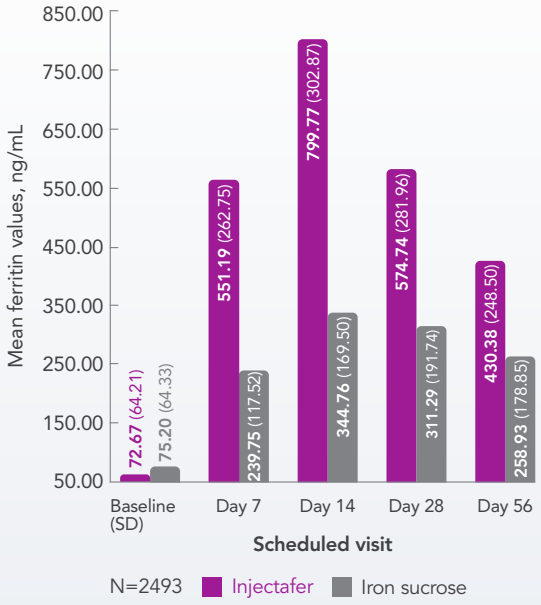
Primary endpoint

Hb: Mean change from baseline to highest value between baseline and day 56 or time of intervention[7,54]

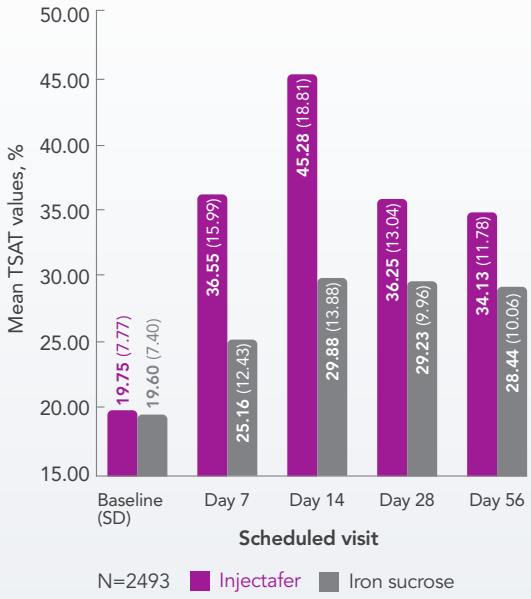


Secondary endpoints (secondary efficacy endpoints were not powered for superiority)[7,54]

Ferritin: Mean value at each scheduled visit



TSAT: Mean value at each scheduled visit



injectafer® ferric carboxymaltose injection

EXPLORING THE EFFICACY AND SAFETY OF INJECTAFER (CONT'D)

The most common adverse reactions in adults (>2%) were nausea, hypertension, flushing, injection site reactions, erythema, hypophosphatemia, and dizziness.[22,53,54]

Adverse reactions reported in ≥1% of patients in adult pivotal trials 1 and 2[22,53,54]

Term	Injectafer, % (n=1775)	Pooled comparators, % (n=1783)	Oral iron, % (n=253)
Nausea	7.2	2	1.2
Hypertension	4	2	0.4
Flushing	4	0.2	0
Injection site reactions	3	3.2	0
Erythema	3	0.6	0
Hypophosphatemia	2.1	0.1	0
Dizziness	2.1	1.3	0.4
Vomiting	2	1	0.4
Injection site discoloration	1.4	0.3	0
Headache	1.3	1.2	0.4
Hepatic enzyme increased	1.2	0.2	0
Dysgeusia	1.2	2.1	0
Hypotension	1	2	0
Rash	1	0.3	0
Constipation	0.5	0.9	3.2

In my facility, we have a robust system with EPIC that definitely helps schedule workflow with order sets and patient referrals. We can also build in parameters to check iron levels if it has not been done in some time.
– Dr. Satheesh Kathula, hematologist/oncologist

SELECTED SAFETY INFORMATION

CLINICAL CONSIDERATIONS IN PREGNANCY

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

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

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

IV IRON INFUSION PROTOCOL: A CLINICAL ROADMAP

Navigating referrals efficiently for your patients with IDA or ID in HF is important for efficient infusions.

Step 1	Obtain iron panels (including ferritin and TSAT) to determine IDA or ID in HF diagnosis
Step 2	Treat with oral iron and assess for efficacy after 14 to 30 days OR treat with Injectafer, if indicated for first-line treatment • Injectafer is first-line in adult patients with IDA and NDD-CKD and ID in HF adult patients[22]
Step 3	Write a prescription for Injectafer and refer the patient to an infusion center (Heme-Onc, outpatient fusion center, or independent infusion center)
Step 4	Utilize Injectafer resources to find an infuser near you • Tools include the infusion center locator and patient education brochures

Streamlined care

Electronic health record (EHR) solutions allow providers to receive the latest evidence-based information directly at the point of care. Contact your DSI representative if interested in EHR implementation.

Embed dosing and administration details for Injectafer into order sets for IDA.

Embed blood tests for iron deficiency directly into your HF order set.

Set up clinical alerts at point of care to test for iron deficiency in appropriate HF patients.

Makes it easy for you to order lab tests for your patients with ID in HF or IDA.

- An alert prompts you to test your patients with ID in HF or IDA and directs you to the order set where lab tests are embedded
- This reminder allows you to focus on patient care and takes the burden off you and your team to remember to routinely test HF patients for iron deficiency

Order set and alert guides include step-by-step instructions that make these updates easy to implement. Updating your EHR can have a powerful impact on how you care for patients.

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KEY TAKEAWAYS AND IMPACT TO CARE

Injectafer is FDA-approved for use in appropriate patients with ID in HF and IDA and provides the most iron per course of treatment in IDA[22,56-60]

ID: approved for appropriate adult patients with NYHA class II/III HF to improve exercise capacity

IDA: first-line with comorbid NDD-CKD; otherwise, patient must prove failure with oral iron therapy

The 4 Ds of Injectafer: data, dosing, delivery, and dilution[22,51-60]

The structure of Injectafer supplies a controlled release of iron, permitting for faster iron repletion in fewer infusions[22,51,52]

Multiple administration options allow patients and providers to tailor Injectafer to their needs, with slow IV push or IV infusion administration in patients[22]

Injectafer has shown efficacy after evaluation in clinical trials

Pivotal trial 1: In cohort 1, Injectafer led to a significantly greater increase in Hb levels from baseline to day 35 compared to oral iron, with a mean (SD) rise of 1.6 (1.2) g/dL versus 0.8 (0.8) g/dL (P=0.001). In cohort 2, Injectafer also demonstrated a greater increase in Hb levels from baseline to day 35 compared to SoC IV iron.

Pivotal trial 2 (REPAIR-IDA): Injectafer 1500 mg demonstrated Hb improvement by day 56 compared to IV iron sucrose 1000 mg. There was no significant difference in the primary composite safety endpoint.[54]

Clinical trials with Injectafer have established a consistent safety profile

Injectafer's clinical trials demonstrate a consistent safety profile across a range of patient populations and treatment settings. These findings may help inform treatment decisions for patients with ID in HF or IDA who are candidates for IV iron therapy[53,54]

Injectafer is contraindicated in patients with hypersensitivity to Injectafer or any of its inactive components. Injectafer can cause serious adverse reactions including hypersensitivity reactions, symptomatic hypophosphatemia, and hypertension.

Please see additional Important Safety Information below. Please see additional Important Safety Information on pages 18-19.

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INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Symptomatic Hypophosphatemia

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

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

Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving Injectafer. Patients may present with shock, clinically significant hypotension, loss of consciousness, and/or collapse.

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

Hypertension

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

Laboratory Test Alterations

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

ADVERSE REACTIONS

Adults

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

Pediatric

The safety of Injectafer in pediatric patients was evaluated in Study 3. Study 3 was a randomized, active-controlled study in which 40 patients (1 to 12 years of age: 10 patients, 12 to 17 years of age: 30 patients) received Injectafer 15 mg/kg to a maximum single dose of 750 mg (whichever was smaller) on Days 0 and 7 for a maximum total dose of 1500 mg; 38 patients evaluable for safety in the control arm received an age-dependent formulation of oral ferrous sulfate for 28 days.

ADVERSE REACTIONS (CONT'D)

The median age of patients who received Injectafer was 14.5 years (range, 1-17); 83% were female; 88% White and 13% Black. The most common adverse reactions (≥4%) were hypophosphatemia (13%), injection site reactions (8%), rash (8%), headache (5%), and vomiting (5%).

Patients with Iron Deficiency and Heart Failure

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

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; *nervous system disorders*: syncope; *respiratory, thoracic and mediastinal disorders*: dyspnea; *skin and subcutaneous tissue disorders*: angioedema, erythema, pruritus, urticaria; *pregnancy*: fetal bradycardia.

CLINICAL CONSIDERATIONS IN PREGNANCY

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

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

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

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To learn more about ID in HF, IDA, and Injectafer, please scan the QR code and complete the form on the page.

Dr. Satheesh Kathula, hematologist/oncologist

Dr. Satheesh Kathula is a board-certified hematologist and oncologist at Premier Health Partners in Dayton, Ohio, and a Clinical Professor of Medicine at Wright State University. He was the President-Elect of the American Association of Physicians of Indian Origin (AAPI) for the 2023-2024 term and serves as the President and Founder of 4CancerWellness, an initiative focused on patient-centered integrative care.

Dr. Kathula completed his residency in internal medicine and fellowship in hematology/oncology at Wright State University. He is a frequent lecturer on lifestyle medicine and has authored numerous abstracts, articles, posters, and book chapters. In recognition of his contributions to the field, he was named "Man of the Year" in 2018 by the Leukemia and Lymphoma Society in Dayton, OH. Dr. Kathula's multifaceted leadership and academic roles underscore his commitment to advancing cancer care through both clinical and holistic approaches.

Click here to see Full Prescribing Information.

Daiichi-Sankyo

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