INDICATIONS AND USAGE
Ferrlecit is an iron replacement product, for treatment of iron deficiency anemia in adult patients and in pediatric patients age 6 years and older with chronic kidney disease receiving hemodialysis who are receiving supplemental epoetin therapy. (1)

DOSEAGE AND ADMINISTRATION

- Adult Patients - The recommended adult dosage is 10 mL (125 mg of elemental iron) diluted in 100 mL of 0.9% sodium chloride administered by intravenous infusion over 1 hour per dialysis session or undiluted as a slow intravenous injection (at a rate of up to 12.5 mg/min) per dialysis session. (2.1)
- Pediatric Patients - The recommended pediatric dosage is 0.12 mL/kg (1.5 mg/kg of elemental iron) diluted in 25 mL 0.9% sodium chloride and administered by intravenous infusion over 1 hour per dialysis session. (2.2)
- Do not mix Ferrlecit with other medications or add to parenteral nutrition solutions for intravenous infusion.
- Administer in 0.9% saline. (2)

DOSEAGE FORMS AND STRENGTHS
Ferrlecit is supplied in a single use vial containing 62.5 mg of elemental iron in 5 mL. (3)

CONTRAINDICATIONS
Known hypersensitivity to sodium ferric gluconate or any of its inactive components. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Monitor patients for signs and symptoms of hypersensitivity during and after Ferrlecit administration for at least 30 minutes and until clinically stable following completion of the infusion. Only administer Ferrlecit when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions. (5.1)
- Hypotension: Ferrlecit may cause hypotension. Monitor patients for signs and symptoms of hypotension during and following each Ferrlecit dose. (5.2)
- Iron Overload: Regularly monitor hematologic responses during Ferrlecit therapy. Do not administer Ferrlecit to patients with iron overload. (5.3)
- Benzyl Alcohol Toxicity: Premature and low-birthweight infants may be more likely to develop toxicity. (5.4)

ADVERSE REACTIONS
The most commonly reported adverse reactions (≥10%) in adult patients were nausea, vomiting and/or diarrhea, injection site reaction, hypotension, cramps, hypertension, dizziness, dyspnea, chest pain, leg cramps and pain. In patients 6 to 15 years of age the most common adverse reactions (≥10%) were hypotension, headache, hypertension, tachycardia and vomiting. (6.1)

Drugs

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis U.S. LLC at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

USF SPECIFIC POPULATIONS

- Pregnancy: Use only if clearly needed (contains benzyl alcohol). (8.1)
- Nursing Mothers: Caution should be exercised when administered to a nursing woman (contains benzyl alcohol). (8.3)
- Pediatric Use: Safety and effectiveness have not been established in pediatric patients <6 years of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2015
5.3 Iron Overload during and following Ferrlecit administration [see Adverse Reactions (6.1)].

5.4 Benzyl Alcohol Toxicity

Ferrlecit contains benzyl alcohol as a preservative. Benzyl alcohol has been associated with serious adverse events and death in pediatric patients. The minimum amount of benzyl alcohol at which toxicity may occur in newborn and low-birth weight infants may be more likely to develop toxicity [see Use in Specific Populations (8.4.)].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Hypersensitivity [see Contraindications (4) and Warnings and Precautions (5.1)].
- Hypotension [see Warnings and Precautions (5.2)].

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The most commonly reported adverse reactions (≥10%) in adult patients were nausea, vomiting and/or diarrhea, injection site reaction, hypotension, cramps, hypertension, dizziness, abnormal erythrocytes (e.g., changes in morphology, color, or number of red blood cells), dyspnea, chest pain, leg cramps and pain. In patients 6 to 15 years of age the most common adverse reactions (≥10%) were hypotension, headache, hypertension, tachycardia and vomiting.

Studies A and B

In multiple dose Studies A and B (total 126 adult patients), the most frequent treatment emergent adverse reactions following Ferrlecit were:

- Body as a Whole: injection site reaction (33%), chest pain (10%), pain (10%), asthenia (7%), headache (7%), fatigue (6%), fever (6%), malaise, infection, abscess, chills, rigors, flu-like syndrome, fever, rigors, fever, chills, generalized weakness.
- Nervous System: cramps (25%), dizziness (13%), paresthesias (6%), agitation, somnolence, decreased level of consciousness.
- Respiratory System: dyspnea (11%), coughing (6%), upper respiratory infections (6%), rhinitis, sneezing.
- Cardiovascular System: hypertension (23%), hypertension (13%), syncope, tachycardia (5%), bradycardia, vasodilatation, anagoria, myocardial infarction, pulmonary edema.
- Gastrointestinal System: nausea, vomiting and/or diarrhea (35%), anorexia, abdominal pain (6%), rectal disorder, dyspepsia, constipation, flatulence, belching, diarrhea, dyspepsia, melena.
- Musculoskeletal System: leg cramps (10%), myalgia, arthralgia, back pain, arm pain.
- Skin and Appendages: pruritus (6%), rash, increased sweating.
- Gynecological System: urinary tract infection, and menorrhagia.
- Special Senses: conjunctivitis, rolling of the eyes, watery eyes, puffy eye lids, arcus senilis, redness of the eye, diplopia, and deafness.

Metabolic and Nutritional Disorders: hyperkalemia (6%), generalized edema (5%), leg edema, peripheral edema, anemia, hypokalemia, hypoglycemia.

Hematologic System: abnormal erythrocytes (11%) (changes in morphology, color, or number of red blood cells), anemia, leukocytosis, lymphadenopathy.

Study C – Pediatric

Pediatric Patients: In a clinical trial of 66 iron-deficient pediatric hemodialysis patients, 6 to 15 years of age, inclusive, who were receiving a stable erythropoietin-dosing regimen, the most common adverse reactions, occurring in ≥25%, regardless of treatment dosage, were: hypotension (35%), headache (24%), hypertension (25%), tachycardia (17%), vomiting (11%), fever (9%), nausea (9%), abdominal pain (9%), diarrhea (8%), anorexia (8%), fatigue (8%), vomiting (8%), anemia (8%), back pain (7%), nasal congestion (7%), respiratory infection (6%), chest pain (6%), dyspnea (6%), diarrhea (6%), and rash (6%).

Hypotension (10%) in adult patients was more common than in children 6 to 15 years of age [see Post Marketing Experience (6.2)].

Post Marketing Experience

In the single-dose, postmarketing safety study, 11% of patients who received Ferrlecit and 9.4% of patients who received placebo reported adverse reactions. The most frequent adverse reactions following Ferrlecit were: hypotension (2%), nausea, vomiting and/or diarrhea (2%), pain (2%), hypertension (0.6%), allergic reaction (0.5%), chest pain (0.5%), pruritus (0.5%), and back pain (0.4%). The following additional events were reported in two or more patients: hypertension, nervousness, dry mouth, and hemorrhage.

In the multiple-dose, open-label surveillance study, 28% of the patients received concomitant angiotensin converting enzyme inhibitor (ACE) therapy. The incidences of both drug intolerance or suspected allergic reactions following first dose Ferrlecit administration were 1.6% in patients with concomitant ACEI use compared to 0.7% in patients without concomitant ACEI use. The patient with a life-threatening reaction to ACE inhibitor (1.8%), had facial flushing immediately on Ferrlecit exposure. No hypotension occurred and the event resolved rapidly and spontaneously without intervention other than drug withdrawal.

The following additional adverse reactions have been identified with the use of Ferrlecit from postmarketing spontaneous reports: anaphylactoid-type reactions, shock, loss of consciousness, convulsion, skin desquamation, palor, phlebitis, dysgeusia, and hypotension.

Individual doses exceeding 125 mg may be associated with a higher incidence and/or severity of adverse reactions [see Post Marketing Experiences (6.2)].

Ferrlecit at elemental iron doses of 125 mg/kg, 78.6 mg/kg, 62.5 mg/kg and 250 mg/kg caused deaths in both mice and rats. Meta-analysis of acute toxicity studies, rabbit and dogs respectively. The major symptoms of acute toxicity were decreased activity, staggering, ataxia, increases in the respiratory rate, tremor, and convulsions.

11 DESCRIPTION

Ferrlecit® (sodium ferric gluconate complex in sucrose injectable), an iron replacement product, is a stable macromolecular complex with an apparent molecular weight on gel chromatography of 289,000 – 440,000, s.d. The macromolecular complex is negatively charged at alkaline pH and is present in solution with sodium cations. The product has a deep red color indicative of ferric oxide linkages. The chemical name is D-Gluconic acid, iron (3+) sodium salt.

Ferrlecit contains benzyl alcohol as a preservative. There are no known adverse outcomes associated with benzyl alcohol, which occurs in manufacturer's iron preparations to help prevent microbial growth. Benzyl alcohol is known to cause serious adverse events and death in pediatric patients. The minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined metabolic load of benzyl alcohol from all sources.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ferrlecit is used to replete the body content of iron. Iron is critical for normal hemoglobin synthesis to maintain an adequate oxygen transport. Additionally, iron is necessary for metabolism and various enzymatic processes.

12.2 Pharmacokinetics

Multiple sequential single dose intravenous pharmacokinetic studies were performed on 14 healthy iron-deficient volunteers. Entry criteria included hemoglobin ≥10.5 g/dL and transfusion saturation ≤15% (TSAT) or serum ferritin value ≤20 mg/mL. In the first stage, each subject was randomized 1:1 to undiluted Ferrlecit injection of either 125 mg/kg or 62.5 mg/kg/0.5 hr (2.1 mg/min). Five days after the first stage, each subject was re-randomized 1:1 to undiluted Ferrlecit injection of either 125 mg/7 min (15.5 mg/min) or 62.5 mg/7 min. Each subject was randomized 1:1 to undiluted Ferrlecit injection of 125 mg/7 min and 62.5 mg/7 min. Each subject was randomized 1:1 to undiluted Ferrlecit injection of 125 mg/7 min and 62.5 mg/7 min.

Peak drug levels (Cmax) varied significantly by dosage and by rate of administration with the highest Cmax observed in the regimen in which 125 mg was administered in 7 minutes (19.0 mg/L). The terminal elimination half-life for drug bound iron was approximately 1 hour. Half-life varied by dose but not by rate of administration. Half-life for undiluted Ferrlecit was 0.85 and 1.45 hours for the 62.5 mg/min and 125 mg/min regimens, respectively, Total clearance of ferric iron was 3.02 to 5.35 L/h. The AUC for ferric iron was 16 mg·hr/L (62.5 mg/kg) to 42 mg·hr/L (125 mg/kg). The major symptoms of acute toxicity were decreased activity, staggering, ataxia, increases in the respiratory rate, tremor, and convulsions.

10 OVERDOSAGE

Ferrlecit is not a dialyzable compound. No data is available regarding overdose of Ferrlecit in humans. Excessive dosages of Ferrlecit may lead to accumulation of iron in storage sites potentially leading to hemosiderosis. Do not administer Ferrlecit to patients with iron overload [see Warnings and Precautions (5.3)].

Individual doses exceeding 125 mg may be associated with a higher incidence and/or severity of adverse events [see Post Marketing Experiences (6.2)].

Ferrlecit at elemental iron doses of 125 mg/kg, 78.6 mg/kg, 62.5 mg/kg and 250 mg/kg caused deaths in both mice and rats. Meta-analysis of acute toxicity studies, rabbit and dogs respectively. The major symptoms of acute toxicity were decreased activity, staggering, ataxia, increases in the respiratory rate, tremor, and convulsions.

In the single-dose, postmarketing safety study, 11% of patients who received Ferrlecit and 9.4% of patients who received placebo reported adverse reactions. The most frequent adverse reactions following Ferrlecit were: hypotension (2%), nausea, vomiting and/or diarrhea (2%), pain (2%), hypertension (0.6%), allergic reaction (0.5%), chest pain (0.5%), pruritus (0.5%), and back pain (0.4%).
and were 9.1 g/dL and 27.3%, respectively, for Ferrlecit-treated patients. Serum iron studies were also similar between treatment and control groups, with the exception of serum ferritin, which was 606 ng/mL for historical control patients, compared to 77 ng/mL for Ferrlecit-treated patients. In this patient population, only the Ferrlecit-treated group achieved increase in hemoglobin and hematocrit from baseline. See Table 2.

**TABLE 2 Study B: Hemoglobin, Hematocrit, and Iron Studies**

<table>
<thead>
<tr>
<th>Mean Change From Baseline to One Month After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrlecit (N=38)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
</tr>
<tr>
<td>Transferin Saturation (%)</td>
</tr>
<tr>
<td>Serum Ferritin (ng/dL)</td>
</tr>
</tbody>
</table>

Study C was a multicenter, randomized, open-label study of the safety and efficacy of two Ferrlecit dose regimens (1.5 mg/kg or 3.0 mg/kg of elemental iron) administered intravenously to 66 iron-deficient (transferin saturation < 20% and/or serum ferritin < 100 ng/mL) pediatric hemodialysis patients, 6 to 15 years of age, inclusive who were receiving a stable epoetin dose regimen. Ferrlecit at a dose of 1.5 mg/kg or 3.0 mg/kg (up to a maximum dose of 125 mg of elemental iron) in 25 mL 0.9% sodium chloride was infused intravenously once every 2 weeks during eight sequential dialysis sessions. Thirty-two patients received the 1.5 mg/kg dose regimen (47% male, 53% female; 66 Caucasian, 25 Hispanic, and 3% Black, Asian, or Other; mean age 12.3 years). Thirty-four patients received the 3.0 mg/kg dose regimen (56% male, 44% female; 77 Caucasian, 12 Hispanic, 9% Black, and 3% Other; mean age 12.0 years). The primary endpoint was the change in hemoglobin concentration from baseline to 2 weeks after last Ferrlecit administration. There was no significant difference between the treatment groups. Improvements in hemoglobin transferrin saturation, serum ferritin, and reticulocyte hemoglobin concentrations compared to baseline values were observed 2 weeks after the last Ferrlecit infusion in both the 1.5 mg/kg and 3.0 mg/kg treatment groups (Table 3).

**TABLE 3 Study C: Hemoglobin, Hematocrit, and Iron Status**

<table>
<thead>
<tr>
<th>Mean Change From Baseline to Two Weeks After Cessation of Therapy in Patients Completing Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrlecit (N=38)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
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<tr>
<td>Transferin Saturation (%)</td>
</tr>
<tr>
<td>Serum Ferritin (ng/mL)</td>
</tr>
<tr>
<td>Reticulocyte Hemoglobin Content (pg)</td>
</tr>
</tbody>
</table>

The increased hemoglobin concentrations were maintained at 4 weeks after the last Ferrlecit infusion in both the 1.5 mg/kg and the 3.0 mg/kg Ferrlecit dose treatment groups.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

NDC 0024-2792-10 for vials

Ferrlecit is supplied in colorless glass vials. Each sterile, single-use vial contains 62.5 mg of elemental iron in 5 mL for intravenous use, packaged in cartons of 10 vials.

Storage

Store at 20 – 25°C (68 – 77°F); excursions permitted to 15 – 30°C (59 – 86°F). See USP Controlled Room Temperature. Do not freeze.

Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

Prior to Ferrlecit administration:

- Question patients regarding any prior history of reactions to parenteral iron products.
- Advise patients of the risks associated with Ferrlecit.
- Advise patients to report adverse reactions associated with the use of Ferrlecit, including hypersensitivity, allergic reactions, dizziness, light-headedness, swelling, and breathing problems (see Warnings and Precautions [5.1, 5.2] and Adverse Reactions [6.1, 6.2]).

Adverse events that Ferrlecit may reduce the absorption of concomitantly administered oral iron preparations [see Drug Interactions (7)].

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