**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.

**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.
- 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.
- Do not mix Ferrlecit with other medications or add to parenteral nutrition solutions for intravenous infusion.
- Administer in 0.9% saline.

**DOSAGE FORMS AND STRENGTHS**

Injection: 62.5 mg/5 mL (12.5 mg/mL) in single-dose vial.

**CONTRAINDICATIONS**

- Known hypersensitivity to sodium ferric gluconate or any of its inactive components.

**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.
- Hypotension: Ferrlecit may cause hypotension. Monitor patients for signs and symptoms of hypotension during and following each Ferrlecit dose.
- Iron Overload: Regularly monitor hematologic responses during Ferrlecit therapy. Do not administer Ferrlecit to patients with iron overload.
- Benzyl Alcohol Toxicity: Premature and low-birth-weight infants may be more likely to develop toxicity.

**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.

**USE IN SPECIFIC POPULATIONS**

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

See 17 for PATIENT COUNSELING INFORMATION.

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nausea). Another 2 patients experienced (0.2%) allergic reactions not deemed to represent drug intolerance (nausea/malaise and nausea/dizziness) following Ferrlecit administration.

5.2 Hypopotension

Ferrlecit may cause clinically significant hypopotension. Hypopotension associated with lightheadedness, malaise, fatigue, weakness or severe pain in the chest, back, flanks, or groin has been observed in association with hypopotension. Hypopotension usually occurs with signs and symptoms of hypersensitivity reactions and usually resolves within one to two hours. In the single-dose safety study, postadministration hypopotensive events were observed in 221/097 patients (2%) following Ferrlecit administration. Transient hypopoten- sion may occur during dialysis. Administration of Ferrlecit may augment hypopotension caused by dialysis. Monitor patients for signs and symptoms of hypopotension during and following Ferrlecit administration [see Adverse Reactions (6.1)].

5.3 Iron Overload

Excessive therapy with parenteral iron can lead to excess storage of iron with the possibility of iatrogenic hemosiderosis. Patients receiving Ferrlecit require periodic moni-
toring of hematologic and iron parameters (hemoglobin, hematocrit, serum ferritin, and transferrin saturation).

5.4 Risk of Serious Adverse Reactions in Infants Due to Benzyl Alcohol Preservative

Ferrlecit is not approved for use in neonates or infants. Serious and fatal adverse reactions including “gassing syndrome” can occur in neonates and low-birth-weight infants treated with benzyl alcohol-preserved drugs, including Ferrlecit. The “gassing syndrome” is characterized by central nervous system depression, metabolic acidosis, and gasping respirations. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known (Ferrlecit contains 9 mg of benzyl alcohol per mL [see Use in Specific Populations (8.4)]).

6 ADVERSE REACTIONS

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

- Hypopotension [see Contraindications (4) and Warnings and Precautions (5.1)]
- Hypopotension [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, hypopotension, cramps, hypertension, dizziness, flushing, rash, pruritus, edema (eye, changes in mouth, tongue, and 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 hypopotension, headache, hypoglycemia and vomiting.

6.2 Postmarketing 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: hypopotension (2%), nausea, vomiting and/or diarrhea (2%), pain (1%), headache (2%), shortness of breath (1%), chest pain (0.5%), fatigue (0.5%), back pain (0.5%). The following additional events were reported in two or more patients: hypertension, nervousness, dry mouth, and hemorhage. In the multiple-dose, open-label surveillance study, 28% of the patients received concomitant antihypertensive/antioxidant enzyme inhibitor (ACEI) therapy. The incidences of drug intolerance or suspected allergic events 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 event was not on ACEI therapy.

One patient had facial flushing immediately on Ferrlecit exposure. No hypopotension 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: anaphylactic-type reactions, shock, loss of vision, and severe hypopotension or shock, superficial thrombophlebitis at injection site, skin discoloration, pallor, phlebitis, dysgeusia, and hypotension.

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

These adverse events included hypopotension, nausea, vomiting, abdominal pain, diarrhea, dizziness, dyspnea, urticaria, chest pain, paresthesia, and peripheral swelling.

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.

7 DRUG INTERACTIONS

Drug-drug interactions involving Ferrlecit have not been studied. Ferrlecit may reduce the efficacy of subcutaneous heparin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Use in Pregnancy Category B

There are no adequate and well-controlled studies with Ferrlecit in pregnant women. Reproduction studies have been performed in mice at doses up to 100 mg/kg/day (300 mg/m²/day) and in rats at up to 20 mg/kg/day (120 mg/m²/day). The doses in mice and rats are 4 and 1.5 times the human dose of 125 mg/day (77 mg/m²/day) on a body surface area basis and have revealed no evidence of harm to the fetus due to Ferrlecit. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Ferrlecit contains benzyl alcohol as a preservative. There are no known adverse outcomes associated with fetal exposure to the preservative benzyl alcohol through maternal drug administration; however, the preservative benzyl alcohol can cause serious adverse events and death when administered intravenously to neonates and infants [see Use in Specific Populations (8.4)].

Ferrlecit adverse reactions including circulatory failure (severe hypotension, shock including in the context of anaphylactic reaction) may occur with Ferrlecit which may have serious consequences on the fetus, such as fetal bradycardia, especially during the second and third trimester.

8.2 Nursing Mothers

It is not known whether Ferrlecit is excreted in human milk. Benzyl alcohol present in maternal serum is likely to cross into human milk and may be orally absorbed by a nursing infant. Caution should be exercised when Ferrlecit is administered to a nursing woman [see Use in Specific Populations (8.4)].

8.4 Pediatric Use

Drug-drug interactions involving Ferrlecit have not been studied. Ferrlecit may reduce the efficacy of subcutaneous heparin.

8.5 Geriatric Use

Clinical studies of Ferrlecit did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

The Ferrlecit iron complex is not dialyzable.

No data is available regarding overdose of Ferrlecit in humans. Excessive dosages of Ferrlecit, as may occur with the use 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 Adverse Reactions (6.2)].

Ferrlecit at elemental iron doses of 125 mg/kg, 78.8 mg/kg, 62.5 mg/kg and 250 mg/kg caused deaths in mice, rats, rabbits, 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 injection), an iron replacement product, is a stable macromolecular complex with an apparent molecular weight on gel chromatography of 289,000–440,000 daltons. 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 oxides linkages. The chemical name is D-Gluconic acid, iron (3+) sodium salt.

The structural formula is considered to be [NaFeO₄(C₆H₇O₇)₆](C₆H₇O₇)₆·H₂O. Ferrlecit is supplied as a clear, dark brown liquid in colorless glass vials. Each 5 mL vial contains 62.5 mg of elemental iron, with 125 mg of sodium ferric gluconate complex in sucrose injection. Ferrlecit is administered intravenously by 40 hours after administration of each dosage regimen. The evaluated population consisted of 39 patients in the low-dose Ferrlecit (sodium ferric gluconate) group (50% female, 50% male; 74% white, 18% black, 1% Hispanic, 9% Other; mean age 12.0 years).

## 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 oxygen transport. Additionally, iron is necessary for metabolism and various enzymatic processes.

### 12.2 Pharmacokinetics

Multiple single-sequence single-dose intravenous pharmacokinetic studies were performed on 14 healthy iron-deficient volunteers. Entry criteria included hemoglobin ≥10.5 g/dL and transferrin saturation ≤15% (TSAT) or serum ferritin value ≤20 ng/mL. In the first stage, each subject was randomized 1:1 to undiluted Ferrlecit injection of either 125 mg/hr or 62.5 mg/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 or 62.5 mg/4 min (>15.5 mg/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 values were 0.85 and 1.45 hours for the 62.5 mg/4 min and 125 mg/7 min regimens, respectively. Total clearance of Ferrlecit was 3.02 to 3.58 L/hr. The AUC for Ferrlecit bound iron varied by dose from 17.5 mg·h/L (62.5 mg) to 35.6 mg·h/L (125 mg). Approximately 80% of drug bound iron was excreted as a monoiron oxovanadate within 24 hours of administration in each dosage regimen. Direct movement of iron from Ferrlecit to transferrin was not observed. Mean peak transferrin saturation returned to near baseline by 40 hours after administration of each dosage regimen.

### 12.3 Inclusion and Exclusion Criteria

Eligibility for this study included chronic hemodialysis patients with a hemoglobin below 10 g/dL (or hematocrit at or below 32%) and either serum ferritin below 100 ng/mL or transferrin saturation below 18%. Exclusion criteria included significant underlying disease or inflammatory conditions or an epoetin requirement of greater than 10,000 units three times per week. Parenteral iron and red cell transfusion were not allowed for two months before the study. Oral iron and red cell transfusion were not allowed during the study for Ferrlecit-treated patients.

The historical control population consisted of 25 chronic hemodialysis patients who received at least eight Ferrlecit doses of either 62.5 mg or 125 mg of elemental iron. A total of 14 patients (37%) completed the study per protocol. Twelve (32%) Ferrlecit-treated patients received less than eight doses, and 12 (32%) patients had incomplete information on the sequence of dosing. Not all patients received Ferrlecit at consecutive dialysis sessions and many received oral iron during the study.

### Table 1: Study A: Hemoglobin, Hematocrit, and Iron Studies

<table>
<thead>
<tr>
<th>Ferrlecit</th>
<th>Mean Change from Baseline to Two Weeks after Cessation of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000 mg IV (N=44)</td>
<td>1.1</td>
</tr>
<tr>
<td>500 mg IV (N=39)</td>
<td>3.6</td>
</tr>
<tr>
<td>*p&lt;0.01 versus the 500 mg group.</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2: Study B: Hemoglobin, Hematocrit, and Iron Studies

<table>
<thead>
<tr>
<th>Ferrlecit (N=38)</th>
<th>Oral Iron (N=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>1.3</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>3.8</td>
</tr>
<tr>
<td>Transferrin Saturation (%)</td>
<td>6.7</td>
</tr>
<tr>
<td>Serum Ferritin (ng/mL)</td>
<td>73</td>
</tr>
</tbody>
</table>

### Study C

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 (transferrin 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 dosing 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 over 1 hour during each hemodialysis session for eight sequential dialysis sessions. Thirty-two patients received 1.5 mg/kg dosing 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 dosing 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 hematocrit, 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></th>
<th>Mean Change from Baseline to Two Weeks after Cessation of Therapy in Patients Completing Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.5 mg/kg Ferrlecit (N=25)</td>
</tr>
<tr>
<td></td>
<td>3.0 mg/kg Ferrlecit (N=32)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>0.8</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>2.6</td>
</tr>
<tr>
<td>Transferrin Saturation (%)</td>
<td>5.5</td>
</tr>
<tr>
<td>Serum Ferritin (ng/mL)</td>
<td>192</td>
</tr>
<tr>
<td>Reticulocyte Hemoglobin Content (pg)</td>
<td>1.3</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
Ferrlecit is a clear, dark brown liquid supplied in colorless glass vials. Each sterile, single-dose vial contains 62.5 mg of elemental iron in 5 mL for intravenous use. Discard unused portion.
Carton containing 10 vials: NDC 0024-2792-10

Storage
Store at 20°C–25°C (68°F–77°F); excursions permitted to 15°C–30°C (59°F–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)].

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