Ferrlecit®

DESCRIPTION
Ferrlecit® (sodium ferric gluconate complex in sucrose injection) is a stable macromolecular complex with an apparent molecular weight on gel chromatography of 280,000 – 440,000 daltons. The macromolecular complex is negatively charged at alkaline pH and is present in an alkaline aqueous solution with approximately 20% sucrose w/v (195 mg/mL) in water for injection, pH 7.7 – 9.7. Each mL contains 9 mg of benzyl alcohol as an inactive ingredient.

CLINICAL PHARMACOLOGY
Ferrlecit is used to replace the total 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.

The total body iron content of an adult ranges from 2 to 4 grams. Approximately 2/3 is in hemoglobin and 1/3 is in reticuloendothelial (RE) storage (bone marrow, spleen, liver) bound to intracellular ferritin. The body highly conserves iron (daily loss of 0.03%) requiring supplementation of about 1 mg/day to replenish losses in healthy, non-menstruating adults. The etiology of iron deficiency in hemodialysis patients is varied and includes blood loss and/or increased iron utilization (e.g., from epoetin therapy). The administration of exogenous epoetin increases red blood cell production and iron utilization. The increased iron utilization and blood losses in the hemodialysis patient may lead to absolute or functional iron deficiency. Iron deficiency is absolute when hematological indicators of iron stores are low. Patients with functional iron deficiency do not meet laboratory criteria for absolute iron deficiency but demonstrate an increase in hemoglobin/hematocrit or a decrease in eosinophilic anemia with stabile iron-mobilization while parenteral iron is administered.

Pharmacokinetics
Multiple single dose single 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 mg/mL. In the first stage, each subject was randomized 1:1 to undiluted Ferrlecit injection of either 125 mg/hr or 62.5 mg/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 initial volume of distribution (Vd) of 6 L corresponds well to calculated blood volume. Vd did not vary by dosage or rate of administration. The terminal elimination half-life (λt) for drug bound iron was approximately 1 hour (λt). Variation by dose but not by rate of administration. The shortest value (0.85 h) occurred in the 62.5 mg/7 min regimen; the longest value (1.45 h) occurred in the 125 mg/7 min regimen. Total clearance of Ferrlecit was 3.02 to 5.35 L/h. There was no significant variation by rate of administration. 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). There was no significant variation by rate of administration. Approximately 80% of drug bound iron was delivered to transferrin as a mononuclear iron species within 24 hours of administration in each dosage regimen. Direct movement of iron from Ferrlecit to transferrin was not observed. Mean peak transferrin saturation did not exceed 100% and returned to near baseline by 40 hours after administration of each dosage regimen.

Pediatrics: Single dose intravenous pharmacokinetic analyses were performed on 48 iron-deficient pediatric hemodialysis patients. Twenty-two patients received 1.5 mg/kg Ferrlecit and 26 patients received 3.0 mg/kg Ferrlecit (maximum dose 125 mg). The mean Cmax, AUC0–t, and terminal elimination half-life values for the 22 patients who received a 1.5 mg/kg dose were 12.9 mg/L, 95.0 mg-h/L, and 2.9 hours, respectively. The mean Cmax, AUC0–t, and terminal elimination half-life values for the 26 patients who received a 3.0 mg/kg dose were 22.9 mg/L, 170.9 mg-h/L, and 2.5 hours, respectively.

In vitro experiments have shown that less than 1% of the iron species within Ferrlecit can be dialyzed through membranes with pores sizes corresponding to 12,000 to 14,000 daltons over a period of up to 270 minutes. Human studies in nennially competent patients suggest the clinical insignificance of urinary excretion.

Drug-drug interactions: Drug-drug interactions involving Ferrlecit have not been studied. However, like other parenteral iron preparations, Ferrlecit may be expected to reduce the absorption of concomitantly administered oral iron preparations.

CLINICAL STUDIES
Two clinical studies (Studies A and B) were conducted in adults and one clinical study was conducted in pediatric patients (Study C) to assess the efficacy and safety of Ferrlecit.

Study A
Study A was a three-center, randomized, open-label study of the safety and efficacy of two doses of Ferrlecit administered intravenously to iron-deficient hemodialysis patients. The study included both a dose-response component and an historical control. Enrolled patients received a test dose of Ferrlecit (25 mg of elemental iron) and were then randomly assigned to receive Ferrlecit at cumulative doses of either 500 mg (low dose) or 1000 mg (high dose) of elemental iron. Ferrlecit was given to both dose groups in eight divided doses during sequential dialysis sessions (a period of 16 to 17 days). At each dialysis session, patients in the low-dose group received 62.5 mg of elemental iron over 30 minutes, and those in the high-dose group received Ferrlecit 125 mg of elemental iron over 60 minutes. The primary endpoint was the change in hemoglobin from baseline to the last available observation through Day 50.

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 mg/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 oral iron supplementation for 14 months and did not receive red cell transfusion. At patients had stable eosinophil and hematocrit values for at least 6 months before the study. The median age of the control patients was 60 years, ranging from 25 to 84 years. 80% were female, 20% were male, and 2% were unknown. Mean age was 56 years, range 20-87 years, and 25 historical control patients (68% female, 32% male; 40% white, 32% black, 4% Hispanic, 4% Asian, 4% unknown; mean age 52 years, range 25–84 years).

The mean baseline hemoglobin and hematocrit were similar between treatment and control patients: 9.8 g/dL and 29% and 9.6 g/dL and 29% in low- and high-dose Ferrlecit-treated patients, respectively, and 9.4 g/dL and 29% in historical control patients. Baseline serum ferritin saturation was 20% in the low-dose group, 16% in the high-dose group, and 14% in the historical control. Baseline serum ferritin was 106 mg/mL in the low-dose group, 88 mg/mL in the high-dose group, and 606 mg/mL in the historical control.

In the high-dose Ferrlecit group achieved significantly higher increases in hemoglobin and hematocrit than patients in the low-dose Ferrlecit group or patients in the historical control group (oral iron). Patients in the low-dose Ferrlecit group did not achieve significantly higher increases in hemoglobin and hematocrit than patients receiving oral iron. See Table 1.

<table>
<thead>
<tr>
<th>TABLE 2 Hemoglobin, Hematocrit, and Iron Studies</th>
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<tr>
<td><strong>Mean Change from Baseline to One Month After Treatment</strong></td>
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<td><strong>Study</strong></td>
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<td><strong>Ferrlecit Dose</strong></td>
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*p < 0.05 versus both the 500 mg group and the historical control group.

Study B
Study B was a single-center, non-randomized, open-label, historically-controlled, study of the safety and efficacy of two doses of Ferrlecit in iron-deficient hemodialysis patients. Ferrlecit administration was identical to Study A. The primary efficacy variable was the change in hemoglobin from baseline to the last available observation through Day 50. Inclusion and exclusion criteria were identical to those of Study A as was the historical control population. Sixty-three patients were entered in this study; 38 in the Ferrlecit-treated group (37% female, 63% male; 95% white, 5% Asian; mean age 56 years, range 22–84 years) and 25 in the historical control group (68% female, 32% male; 40% white, 32% black, 20% Hispanic, 4% Asian, 4% unknown; mean age 52 years, range 25–84 years).

Ferrlecit-treated patients were considered to have completed the study per protocol if they received at least 60 mg of elemental iron or had reached 8 doses with doses of either 125 mg or 62.5 mg. 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.

Baseline hemoglobin and hematocrit values were similar between the treatment and control groups, and were 9.1 g/dL and 27.2%, 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 mg/mL for historical control patients, compared to 77 mg/mL for Ferrlecit-treated patients.

In this patient population, only the Ferrlecit-treated group achieved significant increase in hemoglobin and hematocrit from baseline. This increase was significantly greater than that seen in the historical oral iron treatment group. See Table 2.

<table>
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<th>TABLE 1 Hemoglobin, Ferrlecit, and Iron Studies</th>
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<td><strong>Mean Change from Baseline to Two Weeks After Cessation of Therapy</strong></td>
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*p < 0.01 versus both the 500 mg group and the historical control group.
Hypersensitivity Reactions: See PRECAUTIONS. In the single-dose, post-marketing, safety study one patient experienced a life-threatening hypersensitivity reaction (diaphoresis, nausea, vomiting, severe lower back pain, dyspnea, and wheezing for 20 minutes) following Ferrlecit administration. Among 1,097 patients who received Ferrlecit in this study, there were 9 patients (0.8%) who had an adverse reaction that, in the view of the investigator, precluded further Ferrlecit treatment (drug intolerance). Three of the reactions were allergic reactions (three cases of urticaria, one case of urticaria and angioedema, and one case of flushing, chills, dyspnea/pain chest, and rash), and two other reactions (hypotension and nausea). Another 2 patients experienced (0.2%) allergic reactions not deemed to represent drug intolerance (nausea/malaise and nausea/dizziness) following Ferrlecit administration. Symptoms in 2 (0.7%) of the 1,034 patients who had prior iron dextran exposure had a sensitivity to at least one form of iron dextran (Infergen® or Dexferin®). The patient who experienced a life-threatening adverse event following Ferrlecit administration during the study had a previous severe anaphylactic reaction to dextran in both forms (Infergen® and Dexferin®). The incidences of both drug intolerance and treatment adverse events following first dose Ferrlecit administration were 1.6% in untreated patients with co-existing ACEI use and 0.6% in patients without prior iron dextran sensitivity compared to 0.8% in patients without prior iron dextran sensitivity. In this study, 26% of the patients received concomitant angiotensin converting enzyme inhibitor (ACEI) therapy. The incidences of both drug intolerance and treatment adverse events following first dose Ferrlecit administration were 2.0% in patients co-administered with ACEI and 0.8% 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 hypotension occurred and the event resolved rapidly and spontaneously without intervention other than drug withdrawal. In multiple dose Studies A and B, no fatal hypersensitivity reactions occurred among the 126 patients who received Ferrlecit. Ferrlecit-associated hypersensitivity events in Study A resulted in premature study discontinuation occurred in three out of a total 88 (3.4%) Ferrlecit-treated patients. The first patient withdrew after the development of pruritus and chest pain following the test dose of Ferrlecit. The second patient, in the high-dose group, experienced nausea, abdominal and flank pain, fatigue and rash following the first dose of Ferrlecit. The third patient, in the low-dose group, experienced a “red biotchy rash” following the first dose of Ferrlecit. Of the 38 patients exposed to Ferrlecit in Study B, none reported hypersensitivity reactions. Many chronic renal failure patients experience cramps, pain, nausea, rash, flushing, and pruritus. In the postmarketing spontaneous reporting system, life-threatening hypersensitivity reactions have been reported rarely in patients receiving Ferrlecit. Hypotension: See PRECAUTIONS. In the single-dose safety study/post-marketing hypotensive event study, in 27/1,097 patients (2.4%) following Ferrlecit administration, hypotension has been reported following administration of Ferrlecit in European case reports. Of the 226 renal dialysis patients exposed to Ferrlecit and reported in the literature, 3 (1.3%) patients experienced hypotensive events, which were accompanied by flushing in two: All completely reversed after one hour without sequelae. Transient hypotension may occur during dialysis. Administration of Ferrlecit may augment hypotension caused by dialysis. Among the 126 patients who received Ferrlecit in Studies A and B, one patient experienced a transient decrease of level of consciousness without hypotension. Another patient discontinued treatment prematurely because of dizziness, lightheadedness, diaphoresis, malaise, and weakness without hypotension that resulted in a 3–4 hour hospitalization for observation following drug administration. The syndrome resolved spontaneously. Laboratory Changes: No differences in laboratory findings associated with Ferrlecit (sodium ferric gluconate complex in sucrose injection) were reported in North American clinical trials when normalized against a National Institute of Health database on laboratory findings in 1,100 hemodialysis patients. Most Frequent Adverse Reactions: In the single-dose, post-marketing safety study, 11% of patients 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 (0.7%), tachypnea (0.6%), allergic reaction (0.3%), chest pain (0.5%), pruritus (0.5%), and rash (0.2%). In this similar adverse event analysis following four-treatment groups, the clinical adverse event profile was similar. However, because of the high baseline incidence of adverse events in the hemodialysis patient population, insufficient number of exposed patients, and limitations inherent to the cross-over, single dose study design, no comparison of event rates between Ferrlecit and placebo treatments can be made. In an aggregate of multiple studies A and B, the most frequent adverse reactions to Ferrlecit were: Body as a Whole: A single injection site reaction (3%), chest pain (10%), pain (10%), anemia (7%), headache (7%), abdominal pain (6%), fatigue (6%), fever (5%), malaise, infection, abscess, back pain, chills, rigors, arm pain, carcinoma, flu-like syndrome, sepsis. Nervous System: cramps (25%), dizziness (15%), paraesthesia (6%), agitation, somnolence. Respiratory System: dyspnea (11%), coughing (6%), upper respiratory infections (6%), rhinitis, pneumonia. Cardiovascular System: hypotension (29%), hypertension (13%), syncope (6%), tachycardia (5%), bradycardia, vasodilatation, angina pectoris, myocardial infarction, pulmonary edema. Gastrointestinal System: nausea, vomiting and/or diarrhea (35%), anorexia, rectal disorder, dyspepsia, eructation, flatulence, gastrointestinal disorder, melena. Musculoskeletal System: leg cramps (10%), myalgia, arthralgia. Skin and Appendage: rash (2%), pruritus, sweating, increased sweating. Genitourinary System: urinary tract infection. Special Senses: conjunctivitis, abnormal vision, ear disorder. Metabolic and Nutritional Disorders: hyperkalemia (6%), generalized edema (5%), leucopenia, thrombocytopenia, hyponatremia, homocystinuria, hyperlipidemia. Hematologic System: abnormally erythrocytes (11%), anemia, leukocytosis, lymphadenopathy. Other Adverse Reactions Observed During Clinical Trials: In the single-dose post-marketing safety study in 1,097 patients receiving Ferrlecit, the following additional events were reported in two or more patients: A double increase in serum bilirubin and a decrease in hemoglobin. Ferrlecit contains benzyl alcohol and therefore should not be used in neonates. Postmarketing Surveillance: The following additional adverse reactions have been identified with the use of Ferrlecit from postmarketing spontaneous reports: dysgeusia, hypoesthesia, loss of consciousness, convulsion, skin discoloration, pallor, phlebitis, and shock. 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.

**OVERDOSAGE**

Dosages in excess of iron needs may lead to accumulation of iron in iron storage sites and hemosiderosis. Periodic monitoring of laboratory parameters of iron storage may assist in recognition of iron accumulation. Ferrlecit should not be administered in patients with iron overload.

Serum iron levels greater than 300 µg/dL may indicate iron poisoning which is characterized by abdominal pain, diarrhea, or vomiting which progresses to pallor or cyanosis, lassitude, drowsiness, hyperventilation due to acidosis, and cardiovascular collapse. Caution should be exercised in interpreting serum iron levels in the 24 hours following the administration of Ferrlecit since many laboratory assays will falsely overestimate serum or transferrin bound iron by measuring iron still bound to the Ferrlecit complex. Additionally, in the assessment of iron overload, caution should be exercised in interpreting serum ferritin levels in the week following Ferrlecit administration since, in clinical studies, serum ferritin exhibited a nonspecific rise which persisted for five days.

The Ferrlecit iron complex is not dialyzable.

Ferrlecit at elemental iron doses of 125 mg/kg, 78.8 mg/kg, 62.5 mg/kg and 250 mg/kg caused deaths to 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.

Individual doses exceeding 125 mg may be associated with a higher incidence and/or severity of adverse events based on information from postmarketing spontaneous reports. These adverse events included hypotension, nausea, vomiting, abdominal pain, diarrhea, dizziness, dyspnea, urticaria, chest pain, pancreatitis, 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.

**DOSAGE AND ADMINISTRATION**

The dosage of Ferrlecit is expressed in terms of mg of elemental iron. Each 5 mL sterile, single-use vial contains 62.5 mg of elemental iron (12.5 mg/mL).

The recommended dosage of Ferrlecit for the repletion treatment of iron deficiency in hemodialysis patients is 10 mL of Ferrlecit (125 mg of elemental iron). Ferrlecit may be diluted in 100 mL of 0.9% sodium chloride administered over 1 hour. Ferrlecit may also be administered undiluted as a slow IV injection (at a rate of up to 12.5 mg/min). Most patients will require a minimum cumulative dose of 1.3 gram of elemental iron, administered over eight sessions at sequential dialysis treatments, to achieve a favorable hemoglobin or hematocrit response. Patients may continue to require therapy with intravenous iron at the lowest dose necessary to maintain target levels of hemoglobin, hematocrit, and laboratory parameters of iron storage within acceptable limits. Ferrlecit has been administered at sequential dialysis sessions by infusion or by slow IV injection during the dialysis session itself.

Data from Ferrlecit postmarketing spontaneous reports indicate that individual doses exceeding 125 mg may be associated with a higher incidence and/or severity of adverse events. See OVERDOSAGE.

Pediatric Dosage: The recommended pediatric dosage of Ferrlecit for the repletion treatment of iron deficiency in hemodialysis patients is 0.12 mL/kg Ferrlecit (1.5 mg/kg of elemental iron) diluted in 25 mL 0.9% sodium chloride and administered by intravenous infusion over 1 hour at eight sequential dialysis sessions. The maximum dosage should not exceed 125 mg per dose.

Note: Do not mix Ferrlecit with other medications, or add to parenteral nutrition solutions for intravenous infusion. The compatibility of Ferrlecit with intravenous infusion vehicles other than 0.9% sodium chloride has not been evaluated. Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever the solution and container permit. Discard unused portion after initial use.

If diluted in saline, use immediately after dilution.

**HOW SUPPLIED**

NDC 0024-2792-10

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

Keep out of the reach of children.

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