CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020955

FINAL PRINTED LABELING

DESCRIPTION

Ferrlecit® (sodium ferric gluconate complex in sucrose injection) is a stable macromolecular complex with an apparent molecular weight on gel chromatography of 350,000 ± 23,000 daltons. The macromolecular complex is negatively charged at alkaline pH and is present in solution with sodium cations. It is free of ferrous ion and dextran polysaccharides. The product has a deep red color indicative of ferric oxide linkages.

The structural formula is considered to be $[NaFe_2O_3(C_6H_{11}O_7)(C_{12}H_{22}O_{11})_5]_{\approx 200}$.

Each ampule of 5 ml of Ferrlecit® for intravenous injection contains 62.5 mg (12.5 mg/ml) of elemental iron as the sodium salt of a ferric ion carbohydrate complex 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.
Therapeutic Class: Hematinic

CLINICAL PHARMACOLOGY

Ferrlecit® is used to replete the total body content of iron. Iron is critical for normal hemoglobin synthesis to maintain oxygen transport. Additionally, iron is necessary for metabolism and synthesis of DNA 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 in reticuloendothelial storage (bone marrow, spleen, liver) and 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 can include increased iron utilization (e.g., from erythropoietin therapy), blood loss (e.g., from fistula, retention in dialyzer, hematologic testing, menses), decreased dietary intake or absorption, surgery, iron sequestration due to inflammatory process, and malignancy. The administration of exogenous erythropoietin 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 hematologic 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 erythropoietin dosage with stable hemoglobin /hematocrit when

parenteral iron is administered.

Pharmacokinetics

Human pharmacokinetic studies have not been performed with Ferrlecit®. *In vitro* experiments have shown that less than 1% of the iron species within Ferrlecit® Injection can be dialyzed through membranes with pore sizes corresponding to 12,000 to 14,000 daltons over a period of up to 270 minutes. These studies were conducted with undiluted Ferrlecit®, and with Ferrlecit® diluted in 0.9% saline or double distilled water.

CLINICAL STUDIES

Two clinical studies were conducted to assess the safety and efficacy 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 concurrent control 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 500mg (low dose) or 1000mg (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 Ferrlecit® 62.5 mg of elemental iron over 30 minutes, and those in the high-dose group received Ferrlecit® 125mg of elemental iron over 60 minutes. The primary endpoint was the change in hemoglobin from baseline to the last available observation through Day 40.

Eligibility for this study included chronic hemodialysis patients with a hemoglobin below 10 g/dl (or hematocrit at or below 30%) and either serum ferritin below 200 ng/ml or iron saturation below 18%. Exclusion criteria included significant underlying disease or inflammatory conditions or an erythropoietin (EPO) 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 only oral iron supplementation for 14 months and did not receive red cell transfusion. All patients had stable EPO doses and hematocrit values for at least two months before initiation of oral iron therapy.

The evaluated population consisted of 39 patients in the low-dose Ferrlecit® group, 44 patients in the high-dose Ferrlecit® group, and 25 historical control patients.

The mean baseline hemoglobin and hematocrit were similar between treatment and historical 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 iron 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 ng/ml in the low-dose group, 88 ng/ml in the high-dose group, and 606 ng/ml in the historical control.

Patients in the high-dose Ferrlecit® group achieved significantly higher increases in hemoglobin and hematocrit than either 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 1
Hemoglobin, Hematocrit, and Iron Studies

Study A	Mean Change from Baseline to Two Weeks After Cessation of Therapy		
	Ferrlecit ® 1000 mg IV (N=44)	Ferrlecit ® 500 mg IV (N=39)	Historical Control-Oral Iron (N=25)
Hemoglobin	1.1 g/dl*	0.3 g/dl	0.4 g/dl
Hematocrit	3.6%*	1.4%	0.8%
Iron Saturation	8.5%	2.8%	6.1%
Serum Ferritin	199 ng/ml	132 ng/ml	NA

*p<0.01 versus both the 500mg 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 variable, cumulative doses of intravenous 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 evaluated in this study: 38 in the Ferrlecit® treated group and 25 in the historical control group.

Ferrlecit® treated patients were considered to have completed the study per protocol if they received at least eight Ferrlecit® doses of either 62.5mg or 125mg 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.

Cumulative Ferrlecit® Dose (mg of elemental iron)	62.5	250	375	562.5	625	750	1000	1125	1187.5
Patients (#)	1	1	2	1	10	4	12	6	1

Baseline hemoglobin and hematocrit values were similar between the treatment and control groups, and were 9.1g/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 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 2
Hemoglobin, Hematocrit, and Iron Studies

Mean Change from Baseline to One Month After Treatment		
	Ferrlecit® (N=38)	Oral Iron (N=25)
	change	change
Hemoglobin (g/dl)	1.3a,b	0.4
Hematocrit (%)	3.8a,b	0.2
Iron Saturation (%)	6.7b	1.7
Serum Ferritin(ng/ml)	73b	-145

a - $p<0.05$ on group comparison by the ANCOVA method
b - $p<0.001$ from baseline by the paired t-test method

INDICATIONS AND USAGE

Ferrlecit® is indicated for treatment of iron deficiency in patients undergoing chronic hemodialysis who are receiving supplemental erythropoetin therapy.

CONTRAINDICATIONS

All anemias not associated with iron deficiency.

Hypersensitivity to Ferrlecit® or any of its inactive components.

WARNINGS

HYPERSENSITIVITY REACTIONS: **POTENTIALLY FATAL HYPERSENSITIVITY REACTIONS CHARACTERIZED BY CARDIOVASCULAR COLLAPSE, CARDIAC ARREST, BRONCHOSPASM, ORAL OR PHARYNGEAL EDEMA, DYSPNEA, ANGIOEDEMA, URTICARIA, OR PRURITUS SOMETIMES ASSOCIATED WITH PAIN AND MUSCLE SPASM OF THE CHEST OR BACK WHICH COULD RESULT IN DEATH HAVE BEEN REPORTED RARELY IN PATIENTS RECEIVING FERRLECIT®. FATAL IMMEDIATE HYPERSENSITIVITY REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH MANY IRON CARBOHYDRATE COMPLEXES. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE APPROPRIATE RESUSCITATIVE MEASURES. ALTHOUGH FATAL REACTIONS HAVE NOT BEEN OBSERVED IN FERRLECIT® CLINICAL STUDIES, INSUFFICIENT NUMBERS OF**

PATIENTS MAY HAVE BEEN ENROLLED TO OBSERVE THIS EVENT. See ADVERSE REACTIONS

FLUSHING AND HYPOTENSION: **HYPOTENSION ASSOCIATED WITH FLUSHING, LIGHTHEADEDNESS, MALAISE, FATIGUE, WEAKNESS OR SEVERE PAIN IN THE CHEST, BACK, FLANKS, OR GROIN HAS BEEN ASSOCIATED WITH RAPID ADMINISTRATION OF INTRAVENOUS IRON. THESE HYPOTENSIVE REACTIONS ARE NOT ASSOCIATED WITH SIGNS OF HYPERSENSITIVITY AND HAVE USUALLY RESOLVED WITHIN ONE OR TWO HOURS. SUCCESSFUL TREATMENT MAY CONSIST OF OBSERVATION OR, IF THE HYPOTENSION CAUSES SYMPTOMS, VOLUME EXPANSION. IN NORTH AMERICAN TRIALS, FERRLECIT® DOSES OF 62.5MG OF ELEMENTAL IRON WERE ADMINISTERED OVER 30 MINUTES, AND DOSES OF 125MG OF ELEMENTAL IRON WERE ADMINISTERED OVER ONE HOUR. THIS RATE OF ADMINISTRATION (2.1 MG/MIN) SHOULD NOT BE EXCEEDED. See ADVERSE REACTIONS**

PRECAUTIONS

General: Iron is not easily eliminated from the body and accumulation can be toxic. Unnecessary therapy with parenteral iron will cause excess storage of iron with consequent possibility of iatrogenic hemosiderosis. Iron overload is particularly apt to occur in patients with hemoglobinopathies and other refractory anemias. Ferrlecit® should not be administered to patients with iron overload.
See OVERDOSAGE

Carcinogenesis, mutagenesis, impairment of fertility: Long term carcinogenicity studies in animals were not performed. Studies to assess the effects of Ferrlecit® on fertility were not conducted, Ferrlecit® was not mutagenic in the Ames test and the rat micronucleus test. It produced a clastogenic effect in an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells.

Pregnancy Category B: Ferrlecit® was not teratogenic at doses of elemental iron up to 100 mg/kg/day (300 mg/m^2/day) in mice and 20 mg/kg/day (120 mg/m^2/day) in rats. On a body surface area basis, these doses were 1.3 and 3.24 times the recommended human dose (125 mg/day or 92.5 mg/m^2/day) for a person of 50 kg body weight, average height and body surface area of 1.46 m^2. There were no adequate and well-controlled studies in pregnant women. Ferrlecit® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Ferrlecit® is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of Ferrlecit® in pediatric patients has not been established. Ferrlecit® contains benzyl alcohol and therefore should not be used in neonates.

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 particular, 51/159 hemodialysis patients in North American clinical studies were aged 65 years of older. Among these patients, no differences in safety or efficacy as a result of age were identified. 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.

ADVERSE REACTIONS

A total of 385 patients on hemodialysis have been exposed to Ferrlecit®. Of these, 159 were patients in North American studies and 226 were European patients described in the medical literature.

Flushing and Hypotension: See WARNINGS

Flushing and hypotension have 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 serious hypotensive events which were accompanied by flushing in two. All completely reversed after one hour without sequelae.

In North American clinical studies the incidence of hypotension in patients who received Ferrlecit® 62.5mg of elemental iron over 30 minutes was similar to the incidence of hypotension in patients who received Ferrlecit® 125mg of elemental iron over 60 minutes (34% vs. 36%).

Ferrlecit is intended to be administered during dialysis during which many patients may experience transient hypotension. Administration of Ferrlecit® may augment hypotension caused by dialysis.

Among the 159 patients evaluated in North American clinical studies, one patient experienced a transient decreased level of consciousness without hypotension. Another patient discontinued treatment prematurely because of dizziness, lightheadedness, diplopia, malaise, and weakness without hypotension that resulted in a 3-4 hour hospitalization for observation following drug administration. The syndrome resolved spontaneously.

Hypersensitivity reactions: See WARNINGS

Although fatal hypersensitivity reactions have not occurred in the 385 patients exposed to Ferrlecit®, insufficient numbers of patients may have been exposed to observe this event. The primary Ferrlecit® associated hypersensitivity events in Study A were Type III reactions that occurred in three out of a total 88 (3.%) Ferrlecit® treated patients and which resulted in premature study discontinuation. 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 blotchy rash" following the first dose of Ferrlecit®. Of the 38 patients exposed to Ferrlecit® in Study B, none reported hypersensitivity reactions. Hypersensitivity reactions were not reported in 33 additional patients treated with maintenance Ferrlecit® in North American studies. This group includes five chronic hemodialysis patients with a history of anaphylaxis to iron dextran who received up to 1000mg of Ferrlecit® without an allergic reaction.

Of the 226 renal dialysis patients exposed to Ferrlecit® and reported in the literature, 2 (0.9%) patients experienced adverse events that recurred on drug rechallenge and prohibited further drug use. These were: (1) malaise, heat, vomiting, and loin pain and (2) intense epigastric pain lasting 3-4 hours.

From a total of 387 Ferrlecit® treated patients in medical reports and North American trials, six patients (1.6%) experienced serious reactions which precluded further therapy with Ferrlecit®.

Adverse Laboratory Changes: No differences in laboratory findings associated with Ferrlecit® were reported in North American clinical trials when normalized against a National Institute of Health database on laboratory findings in 1,100 hemodialysis patients.

Other Adverse Events Observed During Clinical Trials: Ferrlecit® has been administered to 159 patients in North American clinical trials. During these trials, all adverse events were recorded by clinical investigators using terminology of their own choosing. Adverse events, whether or not related to Ferrlecit® administration, reported in >1% of Ferrlecit® treated patients from trials A and B are categorized below by body system using modified COSTART terminology and ranked in order of decreasing frequency within each system. Hemodialysis patients may have similar symptoms related to dialysis itself or to chronic renal failure.

Body as a Whole: injection site reaction, pain, chest pain, asthenia, headache, abdominal pain, fatigue, fever, malaise, infection, back pain, rigors, chills, arm pain, flu-like syndrome, sepsis, c(a)arcinoma.

Nervous System: cramps, dizziness, leg cramps, paresthesias, agitation, insomnia, somnolence.

Respiratory: dyspnea, coughing, upper respiratory infections, rhinitis, pneumonia.

Cardiovascular System: hypotension, hypertension, syncope, tachycardia, bradycardia, angina pectoris, myocardial infarction, pulmonary edema.

Gastrointestinal System: nausea, vomiting, diarrhea, rectal disorder, dyspepsia, eructation, flatulence, melena.

Musculoskeletal System: myalgia, arthralgia.

Skin and Appendages: pruritus, increased sweating, rash.

Genitourinary System: urinary tract infection.

Special Senses: conjunctivitis, abnormal vision

Metabolic and Nutritional Disorders: hyperkalemia, generalized edema, leg edema, hypoglycemia, hypokalemia, edema, hypervolemia.

Hematologic System: abnormal erythrocytes, anemia, lymphadenopathy.

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 levels storage may assist in recognition of iron accumulation. Ferrlecit® should not be administered in patients with iron overload.

Serum iron levels greater than 300µg/dL (combined with transferrin oversaturation) 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. Symptoms attributed to oversaturation of transferrin following rapid IV infusions of Ferrlecit® have been reported in two patients.

The Ferrlecit® iron complex is not dialyzable.

Ferrlecit® at elemental iron doses of 125mg/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.

DOSAGE AND ADMINISTRATION

The dosage of Ferrlecit® is expressed in terms of mg of elemental iron. Each 5ml ampule contains 62.5mg of elemental iron (12.5mg/ml).

Before initiating therapeutic doses of Ferrlecit®, administration of an intravenous test dose of 2ml Ferrlecit® (25 mg of elemental iron) is recommended. This test dose should be diluted in 50ml of 0.9% sodium chloride for injection and administered over sixty minutes.

The recommended dosage of Ferrlecit® for the repletion treatment of iron deficiency in hemodialysis patients is 10ml of Ferrlecit® (125mg of elemental iron) diluted in 100 mL of 0.9% sodium chloride for injection, administered by intravenous infusion over 1 hour. Most patients will require a minimum cumulative dose of 1.0 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 Ferrlecit® or other intravenous iron preparations at the lowest dose necessary to maintain the target levels of hemoglobin, hematocrit, and laboratory parameters of iron storage within acceptable limits.

Ferrlecit® has been administered at sequential dialysis sessions by infusion during the dialysis session itself.

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 for injection has not been evaluated. Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever the solution and container permit.

Use immediately after dilution in saline.

HOW SUPPLIED

Ferrlecit® is supplied in colorless glass ampules containing a viscous dark red solution with no visible particulate matter. Each ampule contains 62.5 mg of elemental iron in 5 mL for intravenous use, packaged in cartons of 10 ampules.

Store at 20 C-25°C (68°F-77°F), excursions permitted to 15-30°C (59-86°F). See USP Controlled Room Temperature.

Caution: Rx Only

[Schein Pharmaceutical, Inc. Logo] [R&D Laboratories, Inc. Logo]