CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-955/S-003

Trade Name: Ferrlecit Injection

Generic Name: Sodium Ferric Gluconate Complex in Sucrose

Sponsor: Watson Laboratories, Inc.

Approval Date: February 2, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-955/S-003

CONTENTS

Reviews / Information Included in this NDA Review.	
Approval Letter	X
Approvable Letter	
Final Printed Labeling	X
Medical Review(s)	X
Chemistry Review(s)	X
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	X
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	X
Administrative and Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-955/ S-003

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-955/S-003

R & D Laboratories, Inc.
Attention: Jur Strobos, M.D.
Vice President, Clinical and Regulatory Affairs
4640 Admiralty Way, Suite 710
Marina del Rey, CA 90292

Dear Dr. Strobos:

Please refer to your supplemental new drug application dated August 2, 2000, received August 2, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferrlecit® (sodium ferric gluconate complex in sucrose injection).

We acknowledge receipt of your submissions dated August 2, September 13, October 5, October 12, October 20, October 27, November 3, November 22, December 7, December 11, 2000 and January 3, January 22, January 24, January 25, and January 30, 2001.

This supplemental new drug application provides for changes to the following sections of the approved package insert: DESCRIPTION, CLINICAL PHARMACOLOGY, CLINICAL STUDIES, WARNINGS, ADVERSE REACTIONS, OVERDOSAGE, AND DOSAGE AND ADMINISTRATION.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-955/S-003." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42

Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Brian Strongin, Project Manager, at (301) 827-7310.

Sincerely,

{See appended electronic signature page}

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

/s/

Lilia Talarico
2/2/01 11:25:05 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-955/S-003

APPROVED LABELING

Ferrlecit®
DESCRIPTION

Ferrlecit® (sodium ferric gluconate complex in sucrose injection) 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 oxide linkages.

The structural formula is considered to be $[NaFe_2O_3(C_6H_{11}O_7)(C_{12}H_{22}O_{11})_5]_{n\approx200}$

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 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 can include 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 epoetin dosage with stable hemoglobin/hematocrit when parenteral iron is administered.

Pharmacokinetics

Multiple sequential single dose intravenous pharmacokinetic studies were performed on 14 healthy iron-deficient volunteers. Entry criteria included hemoglobin ≥10.5 gm/dL and transferrin saturation ≤15% (TSAT) or serum ferritin value ≤20 ng/mL. In the 1st stage, each subject was randomized 1:1 to undiluted Ferrlecit® injection of either 125 mg/hr or 62.5 mg/½ hr (2.1 mg/min). Five days after the 1st 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 (C_{max}) varied significantly by dosage and by rate of administration with the highest C_{max} observed in the regimen in which 125 mg was administered in 7 minutes (19.0 mg/L). The initial volume of distribution (V_{Ferr}) of 6 L corresponds well to calculated blood volume. V_{Ferr} did not vary by dosage or rate of administration. The terminal elimination half-life (λ_z-HL) for drug bound iron was approximately 1 hour. λ_z-HL varied by dose but not by rate of administration. The shortest value (0.85 h) occurred in the 62.5 mg/4 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 17.5mg-h/L (62.5 mg) to 35.5 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 ionic 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.

In vitro experiments have shown that less than 1% of the iron species within Ferrlecit® can be dialyzed through membranes with pore sizes corresponding to 12,000 to 14,000 daltons over a period of up to 270 minutes. Human studies in renally competent subjects 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 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 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 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 Ferrlecit® 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 40.

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 only oral iron supplementation for 14 months and did not receive red cell transfusion. All patients had stable epoetin 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 transferrin 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%
Transferrin Saturation	8.5%	2.8%	6.1%
Serum Ferritin	199 ng/mL	132 ng/mL	NA

*p<0.01 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 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 62.5 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.

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 9.1 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 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		
Study B	Ferrlecit® (N=38)	Oral Iron (N=25)
	change	change
Hemoglobin (g/dL)	1.3a,b	0.4
Hematocrit (%)	3.8a,b	0.2
Transferrin 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 anemia in patients undergoing chronic hemodialysis who are receiving supplemental epoetin therapy.

CONTRAINDICATIONS

- All anemias not associated with iron deficiency.
- Hypersensitivity to Ferrlecit® or any of its inactive components.
- Evidence of iron overload.

WARNINGS

Hypersensitivity reactions have been reported with injectable iron products. See PRECAUTIONS.

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.

Hypersensitivity Reactions: Serious hypersensitivity reactions have been reported rarely in patients receiving Ferrlecit®. One case of a life-threatening hypersensitivity reaction has been observed in 1,097 patients who received a single dose of Ferrlecit® in a post-marketing safety study. Three serious hypersensitivity reactions have been reported from the spontaneous reporting system in the United States. See ADVERSE REACTIONS.

Hypotension: Hypotension associated with light-headedness, malaise, fatigue, weakness or severe pain in the chest, back, flanks, or groin has been associated with 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. See ADVERSE REACTIONS.

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 have 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 or 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

Exposure to Ferrlecit® has been documented in over 1,400 patients on hemodialysis. This population included 1,097 Ferrlecit®-naive patients who received a single-dose of Ferrlecit® in a placebo-controlled, cross-over, post-marketing safety study. Undiluted Ferrlecit® was administered over ten minutes (125 mg of Ferrlecit® at 12.5 mg/min). No test dose was used. From a total of 1,498 Ferrlecit®-treated patients in medical reports, North American trials, and post-marketing studies, twelve patients (0.8 %) experienced serious reactions which precluded further therapy with Ferrlecit®..

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 1097 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® administration (drug intolerance). These included one life-threatening reaction, six allergic reactions (pruritus x2, facial flushing, chills, dyspnea/chest pain, 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.

Seventy-two (7.0%) of the 1034 patients who had prior iron dextran exposure had a sensitivity to at least one form of iron dextran (INFeD® or Dexferrum®). 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 –(INFeD® and Dexferrum®). The incidence of both drug intolerance and suspected allergic events following first dose Ferrlecit® administration were 2.8% in patients with prior iron dextran sensitivity compared to 0.8% in patients without prior iron dextran sensitivity.

In this study, 28% of the patients received concomitant angiotensin converting enzyme inhibitor (ACEi) therapy. The incidences of both 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 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 resulting 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 blotchy 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.

Three cases of serious hypersensitivity reactions have been reported from the spontaneous reporting system in the United States.

Hypotension: See PRECAUTIONS. In the single dose safety study post administration hypotensive events were observed in 22/1097 patients (2%) following Ferrlecit® administration. Hypotension has also 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 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.

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.

Most Frequent Adverse Reactions: In the single-dose, post-marketing 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 (0.7%), hypertension (0.6%), allergic reaction (0.5%), chest pain (0.5%), pruritus (0.5%) and back pain (0.4%). Similar adverse reactions were seen following placebo administration. 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 multiple-dose Studies A and B, the most frequent adverse reactions following Ferrlecit® were:

Body as a Whole: injection site reaction (33%), chest pain (10%), pain (10%), asthenia (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 (13%), paresthesias (6%), agitation, somnolence.

RespiratorySystem: 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 Appendages: pruritus (6%), rash, increased sweating.

Genitourinary System: urinary tract infection.

Special Senses: conjunctivitis, abnormal vision, ear disorder.

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

Hematologic System: abnormal 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: hypertonia, nervousness, dry mouth, and hemorrhage.

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 non-specific 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.

DOSAGE AND ADMINISTRATION

The dosage of Ferrlecit® is expressed in terms of mg of elemental iron. Each 5mL ampule 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 by intravenous infusion 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 1.0 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 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.

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.

If diluted in saline, use immediately after dilution.

HOW SUPPLIED

NDC# 0364-2791-23

Ferrlecit® is supplied in colorless glass ampules. 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°C – 30°C (59°F-86°F). Do not freeze. See USP Controlled Room Temperature.

Caution: Rx Only

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-955/S-003

MEDICAL REVIEW(s)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	20-955 (SE8-033: BM, BZ)
Sponsor:	R & D Laboratories, Inc.
Drug name:	Ferrlecit® (sodium ferric gluconate complex in sucrose injection)
Date submitted:	August 2, 2000; September 13, 2000; October 5, 2000; October 20, 2000; October 27, 2000; November 22, 2000; January 24, 2001; January 25, 2001
Date assigned:	August 23, 2000
Review completed:	December 21, 2000
Medical Reviewer:	Min Lu, M.D., M.P.H.

Table of Contents

List of Abbreviations

Abbreviation	Definition
ACE	Angiotensin Converting Enzyme
AE	Adverse Event
COSTART	Coding System for a Thesaurus of Adverse Reaction Terms
CRF	Case Report Form
CRO	Clinical Research Organization
ECG	Electrocardiogram
ESRD	End-Stage Renal Disease
HD	Hemodialysis
ITT	Intent-to-Treat Population
Kt/V	A Dimensionless Index Used to Assess Adequacy of Dialysis
LAE	Life-Threatening Adverse Event
NKF	National Kidney Foundation
NSS	Normal Saline Solution
SAE	Serious Adverse Event
TSAT	Percent Transferrin Saturation
URR	Urea Reduction Ratio

SUMMARY

1. Recommendations

1). The request

) one life-threatening event due to hypersensitivity reaction was reported based on study FER9803 interim analysis, and (2) five life-threatening events due to hypersensitivity reactions have been reported from post-marketing spontaneous reports in United States.

2). The request

(1) There were major differences in study population, study design, study drug regimen, and outcome assessment between the published iron dextran studies and current Ferrlecit study

(2)

(3) The submitted support is a single study without concurrent iron dextran control

3). The request

(1) Incidence rates of events with both treatments (Ferrlecit and placebo) were low in study FER9803. Due to lack of concurrent active treatment control, it is impossible to validate the event identification in the study

(2) The short washout period (2 days) in study FER9803 makes the comparison of adverse events between Ferrlecit and placebo inappropriate because of possible carryover effect.

(3) Ferrlecit is labeled for repeat dosing. Safety information from a single dose safety study (FER9803) may not be representative of allergic event or adverse events occurring with repeat dose administration.

(4) [redacted]

[redacted]

4). The request to delete test dose recommendation in Dosage and Administration section should be approved.

5). The request to add an alternative method of administration by slow injection over 10 minutes should be approved.

6). The request to remove flushing and hypotension reactions from the Warnings section in labeling should be approved (with recommendation of these reactions being included in Precautions section).

2. Summary of Clinical Findings:

Ferrlecit is approved for treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy. The sponsor has submitted a supplement for Ferrlecit to request labeling changes for safety and drug administration for the approved indication.

The proposed labeling changes are:

1). Warnings

[redacted]

(2) Flushing and hypotension reactions associated with rapid drug administration.

2). Clinical Studies

[redacted]

3). Adverse Reactions

Deletion of [redacted] Addition of adverse events following Ferrlecit and placebo based on Study FER9803. Addition of the most commonly-occurring adverse reactions based on study FER9803 interim analysis.

4). Dosage and Administration

Deletion of test dose recommendation and addition of undiluted slow IV push at a rate of up to 12.5 mg/min as an alternative drug dosing regimen.

One clinical trial (FER9803) interim analysis was submitted to support the above labeling changes.

FER9803 is a multicenter, randomized, double-blinded, crossover, single dose, and placebo-controlled study of the safety of Ferrlecit® in hemodialysis patients with iron deficiency anemia. Ferrlecit 125 mg was administered by undiluted slow injection over 10 minutes (12.5 mg/min). No test dose was used. The primary safety endpoints were life-threatening events, drug intolerance events and allergic events. This study is ongoing currently and is expected to enroll 2700 hemodialysis patients. This interim analysis report contains results from 1106 hemodialysis patients with iron deficiency anemia.

Hypersensitivity reactions

There was one case of a life-threatening hypersensitivity reaction reported in the interim analysis of FER9803 and there have been 5 other cases of life-threatening events due to hypersensitivity reactions reported from post-marketing spontaneous adverse event report system between February 18, 1999 (approval date) and October 5, 2000.

Flushing and hypotension reactions

In study FER9803 interim analysis, no event of serious flushing and hypotension reactions has been reported following Ferrlecit administration. There have been 2 cases of flushing and hypotension reactions reported from literature and 2 additional cases reported from spontaneous report system in U.S. This reviewer recommends flushing and hypotension reactions may be moved from the Warnings section to its Precautions section.

The incidence of life-threatening events was 0.09% (95% CI: 0-0.51%) in study FER9803 and 0.61±0.13% in historical control. The incidence of drug intolerance events was 0.82% (95% CI: 0.38-1.55%) in study FER9803 and 2.37±0.31% in historical control.

There were major differences in study design, study population, study drug regimen, frequency of exposure, and outcome assessment between 4 published iron dextran studies and the current Ferrlecit study. These differences are summarized in the following table:

Differences between the published iron dextran studies and FER9803

Differences	**Hamstra** (N=481)	**Fishbane** (N=573)	**Feridex** (N=2240)	**Faich** (N=474)	**FER9803** (N=1106)
Design	Prospective	Retrospective	Prospective	Retrospective	Prospective
Study period	1962-1970	1993-1995	1988-1992	1996	1999
Population	General iron deficiency anemia patients	Hemodialysis patients	Suspected liver disease undergoing MRI	Hemodialysis patients	Hemodialysis patients
Iron dextran formulation/ Ferrlecit	Imferon: withdrawn in 1991	INFed	Feridex: contrast agent for MRI of liver	Unspecified iron dextran	Ferrlecit
Outcome assessment: Life-threatening event Drug Intolerance event	Life-threatening immediate anaphylactoid reactions Discontinued due to severe reactions	Severe reactions Discontinued due to adverse events	Anaphylactic and allergic adverse events Discontinued infusion because of acute, moderate to severe pain	Use of iron dextran and epinephrine during the same hospital stay Unavailable	Any immediate hypotensive/ respiratory reaction which were not immediately (<10 minutes) responsive to the interventions. Any event that was sufficient to preclude re-exposure to the drug substance.
Number of dose exposure	4-5 doses	10 doses	1 dose	unspecified	1 dose

Reviewer's table

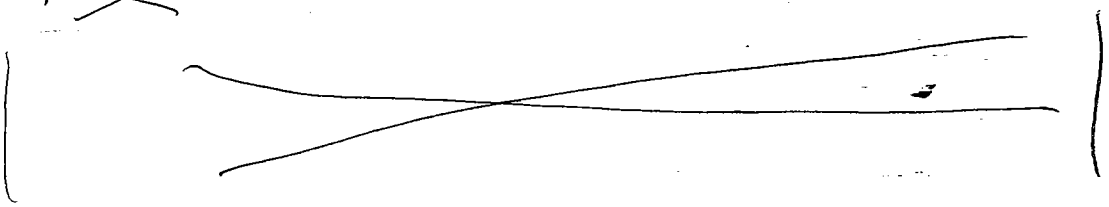
Based on the interim analysis of FER9803,

The incidence of suspected allergic event was 0.82 (95% CI: 0.38-1.55%) following Ferrlecit administration and 0.36% (95% CI: 0.10-0.93%) following placebo administration in FER9803 interim report. The incidence of all adverse events was 11.2% following Ferrlecit administration and 9.4% following placebo administration.

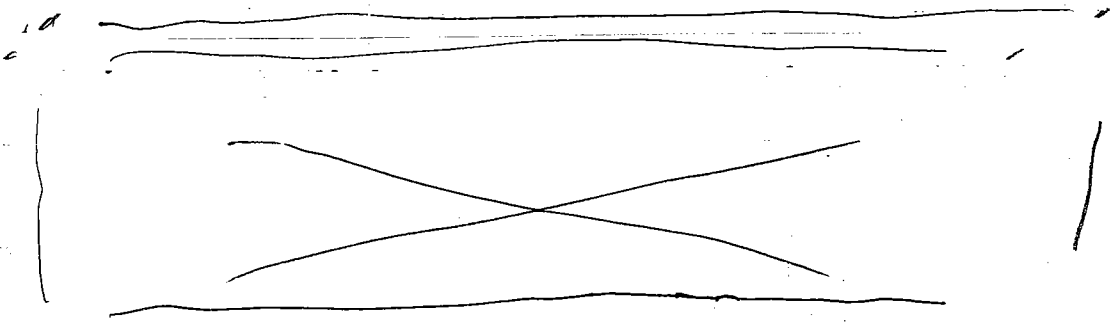
The comparison between Ferrlecit and placebo in regard to allergic events or all adverse events is inappropriate

1) Incidence rates of events with both treatments (Ferrlecit and placebo) were low in study FER9803.

2) This study was a crossover study with only 2-day washout period between Ferrlecit and placebo. The comparison was made between overall Ferrlecit and overall placebo in the same population. Carry-over effects, including adverse events, of Ferrlecit could occur in patients following placebo administration



Life-threatening hypersensitivity reactions have been reported in the study FER9803 (one case) and from post-marketing spontaneous report system , in United States since its approval in February 1999. This important safety information should be presented in Adverse Reactions section, as well as in Warnings section. Flushing and hypotension reactions associated with rapid administration could be presented in precautions section.



Deletion of test dose recommendation and addition of undiluted slow IV push at a rate of up to 12.5 mg/min as an alternative doing regimen.

In study FER9803, Ferrlecit has been administered at dose of 125 mg of elemental iron given by slow injection over 10 minutes without a test dose in 1097 hemodialysis patients. Generally, these patients tolerated this administration well. This reviewer recommends that Ferrlecit may be administered without test dose by slow injection as in study FER9803.

1. Introduction and Background

The sponsor has submitted a supplement for Ferrlecit to request labeling changes for safety and drug administration for the approved indication.

Ferrlecit (sodium ferric gluconate complex in sucrose injection) was approved for treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy on February 18, 1999 (NDA 20-955). The sponsor agreed to perform Phase IV studies to provide additional safety data (e.g., incidence of allergic or anaphylactic reactions, cross-reactivity with other parenteral iron preparations) for Ferrlecit for the approved indication.

Study FER9803 is one of the Phase IV studies that the sponsor is currently conducting to evaluate the safety of Ferrlecit. This study is expected to enroll 2700 hemodialysis patients with iron deficiency anemia and is scheduled to be completed in February, 2001.

To support the request labeling changes in this supplement, the sponsor has submitted the interim analysis results of Study FER9803.

The proposed labeling changes are:

1). Warnings

(2) Flushing and hypotension reactions associated with rapid drug administration.

2). Clinical Studies

(1)

(2)

3). Adverse Reactions

Deletion Addition of adverse events following Ferrlecit and placebo based on Study FER9803. Addition of the most commonly-occurring adverse reactions based on study FER9803 interim analysis.

4). Dosage and Administration

Deletion of test dose recommendation and addition of undiluted slow IV push at a rate of up to 12.5 mg/min as an alternative drug dosing regimen.

2. Material reviewed

Volume	Contents	Submission date	Receipt date
38.1	Proposed labeling change	08/02/2000	08/02/2000
38.5-38.10	FER9803 interim analysis report and clinical data		
39.1	Expedited review request	08/02/2000	08/04/2000
40.1	Post-marketing data	09/13/2000	09/13/2000
41.1	Subgroup analysis	10/05/2000	10/05/2000
BM	Responses	10/20/2000	10/20/2000
BM	Responses	10/22/2000	10/27/2000
BM	Responses	10/27/2000	10/27/2000
BM	Responses	11/22/2000	11/27/2000

Reviewer's table

3. Study FER9803

3.1 Study Protocol

Title of the Study
Crossover, Randomized, Blinded, Prospective, Multicenter Clinical Evaluation of The Rate of Adverse Events to Ferrlecit® in Hemodialysis Patients as Compared to Placebo and Historical Controls.

3.1.1 Study Objectives
Primary Objectives

- To compare events defined as Outcome Adverse Events (Outcome AEs) and Life-threatening Adverse Events (LAEs) after Ferrlecit administration to two controls: (1) Outcome AEs and LAEs after placebo; (2) to the same defined events identified from an historical control after iron dextran administration.
- To compare the incidence of all allergic reactions following Ferrlecit® administration and those following placebo administration.
- To assess the safety of administration of Ferrlecit® at a rate of 12.5 mg/min (the rate generally used in Europe).

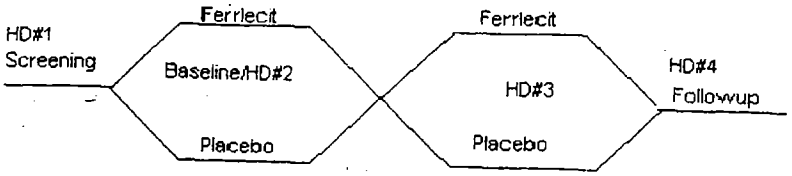
Secondary Objectives

- To determine the rate of all adverse events following Ferrlecit® administration.
- To compare the incidence of all adverse events following Ferrlecit® administration and those following placebo administration.
- To evaluate the safety of therapeutic administration of Ferrlecit®.
- To evaluate changes in tryptase concentrations in the hemodialysis patient and from pre- to post-treatment levels in patients with clinical signs and symptoms of allergic reactions.
- To compare the incidence of all allergic adverse events in Ferrlecit® treated patients receiving concomitant angiotensin converting enzyme (ACE) inhibitor therapy and patients not receiving such treatment.

3.1.2 Study Design

This was a multicenter, randomized, double-blinded, crossover, single dose, placebo-controlled study of the safety of Ferrlecit® in hemodialysis patients with iron deficiency anemia. The safety results of Ferrlecit in this study were compared to iron dextran in historical control identified from a meta-analysis of publications. The following figure shows the schematic chart of the study design. The total study duration was approximately 1 week from screening (first hemodialysis session, HD#1) to follow-up hemodialysis session (HD#4).

Figure 1 Study Design Schematic



Sponsor's chart in NDA Vol. 38.5, pp. 34

3.1.3 Study Population

Inclusion Criteria

- Adult male or female hemodialysis patient who can provide written informed consent;
- On supplemental erythropoietin therapy for >120 days;
- Physician identified need for at least 125 mg of elemental intravenous iron as defined by: Hematocrit <36% or hemoglobin <12.5 gm/dL; serum apoferritin <800 nWmL and transferrin saturation <50% (values should be obtained within the week preceding HD#2);
- Chronic hemodialysis for >120 days for a diagnosis of End Stage Renal Disease; and,
- Ability and willingness to cooperate with the study design parameters including 2 sequential drug administrations.

Exclusion Criteria

- Prior treatment with Ferrlecit®;
- Known sensitivity to benzyl alcohol;
- First use of a dialyzer membrane;
- Acute or chronic therapy with antihistamines or corticosteroids. These agents may blunt or inhibit laboratory indicators of immunologically-mediated reactions;
- Clinical instability defined as:
  - Dialysis for fluid removal at a rate of >1 L/hour;
  - Kt/V <1.2 or URR<65%;
  - Serum albumin ≤3.0 gm/dL;
  - History of repeated missed dialysis sessions in last three months;
  - Presence of signs or symptoms or undergoing acute therapy for an infectious disease;
  - Presence of an active malignancy;
  - Suspicion or presence of unstable angina;
  - History of stroke or other symptoms of cerebral vascular insufficiency;

- Inability to achieve normal oxygen saturation;
- Any blood sugar >400 mg/dL or < 50 mg/dL in preceding two weeks;
- Hospitalization within 30 days of HD session #1 (except for vascular access repair);
- Use of an Investigational Agent within 7 days of HD session # 1.

3.1.4 Study Drug

Ferrlecit® (sodium ferric gluconate complex in sucrose) was supplied as a deep red, sterile liquid for intravenous injection in 5 mL single dose ampules. Each ampule contained 62.5 mg of elemental iron (12.5 mg/ml).

Placebo was supplied in single dose vials consisting of sterile saline with 9 mg/mL benzyl alcohol.

During a treatment session, 10 mL of Ferrlecit® (125 mg of elemental iron) or placebo was administered by slow injection over 10 minutes via the venous return line using a syringe that had been covered for blinding purpose. Treatment was administered during the first hour of hemodialysis.

Antihistamines and corticosteroids (including inhalers), which may blunt or inhibit laboratory indicators of immunologically-mediated reactions, were prohibited during the study.

3.1.5 Study Plan

The following table shows the study schedule:

	HEMODIALYSIS SESSION[1]			
Procedure	**Before or at #1**	**#2**	**#3**	**#4**
Informed Consent	X			
Medical History	X			
Concomitant Medication Review	X	X	X	X
Physical Exam	X			
Eligibility Assessment	X	X		
Blood Draws	X[2]	X[3, 4, 5]	X[4,5]	
1st Infusion		X		
2nd Infusion			X	
Vital Signs		X	X	
Record Duration of HD Session		X	X	
AE Assessment		X[6]	X[6,7]	X[7]

[1] Session #2, #3, and #4 must be consecutive sessions. If greater than one week elapses between HD session #1 and #2, clinical labs and eligibility evaluation must be repeated.
[2] Review clinical laboratories obtained for patient.
[3] In a selected group of 200 of the initial patients, pre- and late dialysis tryptase assays will be run.
[4] Baseline tryptase level.
[5] Post-event tryptase level if a potential allergic adverse event occurs.
[6] AEs will be assessed during and after infusion.
[7] Before initiating dialysis, AEs will be assessed since the prior HD session.

Sponsor's table in NDA Vol. 38.5, IV.E.1.a) (i), appendix B

Patients who sign the informed consent and satisfy the selection criteria were eligible to enter the study and participate over the course of four sequential dialysis sessions with a duration of approximately 1 week from a first hemodialysis session through the subsequent three hemodialysis sessions. Patients were randomly allocated using a 1:1 ratio to 2 groups at HD#2: initial treatment with Ferrlecit or with placebo. Each patient was then crossed over to the alternate treatment during the next hemodialysis session.

Observations at 5 and 15 minutes after initiation of the injection at HD#2 and HD#3 for signs and symptoms of a possible allergic reaction were to be recorded.

Vital signs were to be recorded before, during and after administration of study drug. Patient signs and symptoms were to be recorded on the case report form (CRF) before and after infusion. Blood pressure and pulse were to be recorded at baseline, at 5 minutes into the injection, and at 5 and 20 minutes after completion of the infusion. In the event that a patient experiences symptoms and/or a hypotensive episode during dialysis, additional measurements were to be obtained as appropriate.

At the beginning of HD#3 and HD#4, patients were to be assessed for any adverse reactions since the preceding HD session at which drug substance had been given. Upon completion of this assessment at HD#4, the study was completed.

Tryptase Assay
The first two hundred patients (from selected centers) were to have serum tryptase assays performed from serum obtained during dialysis. Blood was drawn during HD#2 prior to and one hour after study drug administration to define the range of normal for tryptase in this patient population and to identify the effect of dialysis, Ferrlecit® administration, and normal saline/benzyl alcohol solution (placebo) administration on circulating tryptase level. In the event that a patient in this subgroup had a potential allergic adverse event, their blood was not be included in the analysis defining the normal range, and a replacement was selected. If this sub-analysis defined a normal tryptase value in the hemodialysis population as undetectable, then a significant increase was defined as any detectable increase in tryptase. If this sub-analysis defined a normal tryptase value in the hemodialysis population as measurable, then a significant increase was defined as an increase which is 2 standard deviations from the mean change defined in the reference (200-patient) population.

In all patients, a baseline serum specimen was obtained at initiation of dialysis on HD#2 and HD#3 before study drug administration. In patients who have a potential allergic adverse event during administration of either placebo or Ferrlecit®, another serum specimen was to be obtained one hour following the beginning of the event. Both baseline and post-event serum specimens were to be sent to a central laboratory for assessment of baseline and change-in-baseline tryptase levels. In patients who do not experience an event, the baseline serum specimen was discarded.

3.1.6 Outcome Assessments

The following events were included in the outcome assessments:
- Outcome Adverse Events
- Life-Threatening Adverse Events
- Allergic Adverse Events

"Outcome Adverse Event" (Outcome AEs)
An outcome adverse event was defined as any of the following events:

1) An event meeting the protocol-specified definition of a **"Life Threatening Adverse Event"** which was defined as:
   - Any immediate hypotensive reaction following drug or placebo administration which required the institution of resuscitative measures which were not immediately (< 10 minutes) responsive to the interventions described in protocol and thus required permanent cessation of drug therapy; OR,
   - Any immediate respiratory reaction following drug or placebo administration which required the institution of resuscitative measures which were not

immediately (< 10 minutes) responsive to interventions and thus required permanent cessation of drug therapy; OR,

2) Another immediate reaction (other than hypotension) that required permanent cessation of drug therapy; OR,
3) Recurrent or persistent hypotension after study drug administration which would preclude future therapeutic administration of the drug product. Such a patient were also to be identified as having a potential non-anaphylaxis allergic AE; OR,
4) A delayed reaction reported at the following HD session that was possibly or probably related to drug administration and that was sufficient to preclude future therapeutic administration of the drug product.

"Allergic Adverse Event"
Allergic adverse events were defined as either non-anaphylaxis or anaphylaxis allergic events confirmed by changes in tryptase assay.

1) Non-anaphylaxis allergic adverse events were defined as:
   - post-administration signs or symptoms of an allergic reaction (rash, pruritus, cramps, abdominal or other acute spasmodic pain, nausea and vomiting); WITH,
   - a significant increase from baseline tryptase level.

2) Anaphylaxis allergic adverse events were defined as:
   - an LAE; WITH,
   - post-administration signs or symptoms of an anaphylactic reaction (bronchospasm, laryngeal edema, rash, pruritis, urticaria) WITH,
   - a significant increase from baseline tryptase level.

Adverse Event
All adverse events and serious adverse events occurring during the period of time between the HD#2 treatment infusion through completion of study at HD#4 were to be recorded on forms and subsequently coded using COSTART terms.

3.1.7 Historical Control of Iron Dextran from Publications

Four publications were included as iron dextran historical control for Ferrlecit in this study. The following table summarizes the study design, study population, iron dextran preparation, and possible life-threatening and drug intolerance events from each publication.

Published Historical Control of Iron Dextran

Published Studies	Study design	Study population	Iron dextran	Life-threatening events	Outcome events (Drug intolerance)
Hamstra (JAMA 243:1726-1731, 1980)	Observational study in 481 patients who received iron dextran between January 1962 to January 1970 Study period: 1/1962-1/1970 Study site: Denver, CO	481 adult patients: 471 iron deficiency due to blood loss and 10 prisoner volunteers Age <55 years: 77% ≥55 years: 23% Male: 38%, Female: 62%	Imferon 250-500 mg at <100 mg/min; 2099 injections	3 (0.62%) patients had life-threatening immediate anaphylactoid reaction: hypotension, syncope, purpura, wheezing, dyspnea, respiratory arrest, and cyanosis, lasting up to one hour and occurring only after the first injection.	9 (1.87%) patients experienced a severe reaction that required permanent discontinuation of iron dextran. These events included 3 life-threatening events and other reactions: arthralgia, myalgia, erythema nodosum, fever, adenopathy, sore neck, and wheezing
Fishbane (AJKD 28: 529-34, 1996)	Retrospective review of medical records from 4 dialysis centers Study period: 7/1993-6/1995 Study sites: Mineola, NY Cleveland, OH Irvine, CA, Iowa City, IA	573 hemodialysis patients Age: 48.6±4.2 years Male: 51%, Female: 49% Race (available in only 866 patients): White: 39% Black: 44% Hispanic: 8% Asian 3% Other 6%	INFed 100 mg per dialysis	4 (0.70%) patients reported severe reactions included cardiac arrest, dyspnea, hypotension and chest pain.	22 (3.84%) patients had adverse events that led to permanent discontinuation of iron dextran. These events included itching, dyspnea or wheezing, chest pain, nausea, hypotension, swelling, skin flushing, cardiac arrest, myalgias
Feridex IV label (Ferumoxides injection solution)	Controlled clinical trial in 2240 subjects Study period: Study sites: United States Japan: Europe	2240 subjects: 32 healthy volunteers and 2208 patients with known or suspected liver lesions. Age: 54.9 years (range 11-89 years); Male: 56% Female: 44% Race: Asian: 75%; White: 22%; Black: 2%; Other: <1%	Feridex 35% received 0.56mg of iron/kg and 62% received a 0.84 mg iron /kg.	11 (0.49%) patients experienced anaphylactic and allergic adverse events (generalized urticaria, respiratory symptoms, and hypotension) that required acute treatment.	33 (2.15%) patients in a subgroup of 1535 patients in the trial discontinued infusion permanently because of acute, moderate to severe pain (back, lower torso, chest, groin or upper leg) with or without hypotension.
Faich (Unpublished data cited in AJKD 33: 464-70, 1999)	Retrospective review of hospital discharge records during a 6-month period in 1996 from a 100-hospital network	474 hemodialysis patients received iron dextran during their hospital stay	Iron dextran (unspecified) Dosage: unknown	5 (1.1%) patients also received epinephrine during the same hospital stay	No data available

Reviewer's table

Reviewer's Comments: *It should be noted that there were differences in study populations, study designs, study drugs, study regimens, and outcome assessment among the 4 studies. These differences make the combination of these study results as the overall results for iron dextran inappropriate. The following summarizes the major problems in each published study that was considered as a historical control for current Ferrlecit study:*

1) *Hamstra publication*

This was a prospective observational study conducted about 30 years ago in general iron deficiency anemia patients (except 10 prison volunteers). The study population was not hemodialysis patients. The study patients were much younger and had more females than those in the current Ferrlecit study. The study drug was Imferon, a formulation of intravenous iron dextran, which was withdrawn from market in 1991 due to safety reasons related to the formulation. The study drug dosage was much higher in this study compared to current iron dextran recommended dose (100 mg) for hemodialysis patients. The drug intolerance events were based on 2099 total drug injections in 481 patients (average 4-5 doses per patients), which was different from current Ferrlecit study based on a single first dose. The majority of events leading to drug intolerance in this publication were different from those included in the current Ferrlecit study. The differences in study population, drug dosage, frequency of drug exposure, and outcome assessment make the Hamsta study as a iron dextran historical control of current Ferrlecit study inappropriate.

2) *Fishbane publication*

Fishbane study was a retrospective review of adverse reactions from medical records in 573 hemodialysis patients. The study drug was INFed. The author indicated that the typical treatment regimen consisted of 10 doses of 100 mg of iron dextran injected during sequential hemodialysis treatments. The severe reactions, life-threatening events considered by the sponsor, and drug intolerance events collected in this study were based on repeat exposure rather than single first dose in current Ferrlecit study. The author reported that only 5 of 22 drug intolerance events, and 4 of 10 anaphylactoid reactions occurred with the initial test dose exposure (25-50 mg). It appears from this publication that outcome events, even for anaphylactoid reaction, were related to frequency of exposure. Therefore, the comparison of adverse events between Fishbane study (repeat doses for 10 doses) and the current Ferrlecit study (single first dose) was inappropriate. The results of the comparison may be biased in favor of Ferrlecit because of single dose drug exposure in Ferrlecit study.

3) *Feridex IV labeling*

Feridex is a colloid of superparamagnetic iron oxide containing dextran. Feridex is approved as a contrast agent prescribed for liver enhancement during MRI only. Feridex has a different molecular weight and different combination of iron and dextran from available iron dextran preparations (INFed and DexFerrum) for treatment of iron deficiency anemia patients. It is unknown if there were different adverse event profiles between Feridex and iron dextran but these two drugs are not interchangeable clinically. The drug dosage was also different between Feridex and recommended iron dextran dosage. The study population in Feridex study included patients with suspected liver

damage undergoing MRI. The events leading to drug intolerance in this publication were acute, moderate to severe pain with or without hypotension, which were different from events included in drug intolerance in the current Ferrlecit study. The different study population, study drug, drug dosage, and outcome assessment between this study and current Ferrlecit study make the Feridex study inappropriate as a iron dextran historical control.

4) *Faich publication*
This was unpublished data cited in Faich's review. The study was a retrospective review of hospital discharge for medication used in 474 hemodialysis patients who received iron dextran. The patients who received epinephrine and iron dextran during the same hospital stay were considered as having a life-threatening event. The study iron dextran dosage and frequency of exposure were unknown. The different criteria used in outcome assessment and unknown frequency of drug exposure make this study as a iron dextran historical control inappropriate.

Because of the above differences between 4 published studies and current Ferrlecit study, interpretation of comparison between overall historical control results and Ferrlecit study will be difficult and results of comparison may not be reliable. In addition, there were no protocols, data listings or study reports provided for these studies. These published historical control studies can be only considered as a reference data for iron dextran (

The following are the sponsor's summary of the life-threatening events and outcome events (drug intolerance) from these 4 publications.

Table 1: Life-Threatening Reactions (defined as death or acute reaction requiring immediate medical intervention) – Woodman omitted

Study	Number Patients	Percent[13] (%)	Standard Deviation (%)	95% Confidence Interval (%)
Hamstra	481	0.62	0.36	0.00 – 1.33
Fishbane	573	0.70	0.35	0.02 – 138
Feridex®	2240	0.49	0.15	0.20 – 0.78
Faich	474	1.05	0.47	0.14 – 1.97

Overall average percent. This is the expected percentage based on all studies.
Percent = 0.61
Standard deviation = 0.13
95% confidence interval = 0.36 – 0.86

Table 2: Severe Reactions (defined as any reaction that requires permanent drug withdrawal) – Woodman Omitted (Outcome Adverse Events for this study)

Study	Number Patients	Percent[14] (%)	Standard Deviation (%)	95% Confidence Interval (%)
Hamstra	481	1.87	0.62	0.66 – 3.08
Fishbane	573	3.84	0.80	2.27 – 5.41
Feridex®	1535	2.15	0.37	1.42 – 2.88
Faich	No data			

Overall average percent. This is the expected percentage based on all studies.
Percent = 2.47
Standard deviation = 0.31
95% confidence interval = 1.87 - 3.07

Sponsor's table in NDA Vol. 38.5, IV.E.1.a) (i), pp. 7

The sponsor proposed to compare the overall average percent rate ± standard deviation (0.61±0.13% for life-threatening events and 2.47±0.31% for outcome events) from the 4 publications with 95% confidence interval of life-threatening event rate and outcome events rate in Ferrlecit study.

Reviewer's Comments: *The sponsor proposed to compare the overall average percent rate ± standard deviation for iron dextran, which was the 68% confidence interval from the 4 publications, to 95% of confidence interval of rates for Ferrlecit from the current study. This may bias the result in favor of finding a result as difference between these two drugs because a narrow confidence interval was used for iron dextran. No rationale was provided in the study protocol for using different confidence interval levels for these two drugs.*

3.1.8 Statistical Methods

The primary analysis group consisted of all patients who entered the study and received at least one treatment (intent-to-treat patient population). A secondary patient population consisted of all patients who receive a study infusions with both Ferrlecit® and placebo (per protocol population).

The **primary analysis** consisted of three event comparisons.

- Outcome adverse events
- Life-threatening adverse events
- Allergic adverse events

With respect to the three outcome analyses, the study results were to be considered positive if any of the comparisons were POSITIVE and none of the other comparisons were NEGATIVE. The study results were to be considered NEGATIVE if any of the comparisons were NEGATIVE.

1) Outcome adverse events and life-threatening adverse events

The sponsor proposed to use following event rates from 4 publications as events rate for iron dextran:

- Outcome adverse events: 2.47±0.31%
- Life-threatening events: 0.61±0.13%

This comparison was to be performed by constructing an exact 95% confidence interval for the event rate for the Ferrlecit® treatment group. The sponsor proposed the following as interpretation of results:

- POSITIVE: If the upper bound of 95% confidence interval for Ferrlecit in this study was found to fall below the lower bound of iron dextran from historical control then it was concluded that this study arm was POSITIVE and the event rate for Ferrlecit® was significantly lower than that for the historical iron dextran rate.

- NEGATIVE: If the lower bound of the 95% confidence interval for Ferrlecit® in the study was found to fall above the upper bound of iron dextran from historical control

then it was concluded that this study arm was NEGATIVE and the event rate for Ferrlecit® was significantly higher than that of iron dextran.

- INDETERMINATE: If the 95% confidence interval for Ferrlecit overlapped 95% confidence interval of iron dextran from historical control then it concluded that the event rate for Ferrlecit® cannot be statistically distinguished from the iron dextran rate.

Reviewer's Comments: *As this reviewer mentioned above, the historical control of iron dextran including 4 publications was inappropriate. The overall results from these 4 publications may not be reliable.*

The Ferrlecit® treatment group was also compared to the placebo group with respect to the event rate using McNemar's test.

2) Allergic adverse events

Ferrlecit was compared to placebo with respect to the rate of allergic adverse events using McNemar's test. An additional comparison between the treatment groups was to be based on Fisher's exact test. If the rate of all allergic reactions to Ferrlecit® was either significantly less than or statistically indistinguishable from placebo the comparison was to be considered POSITIVE. If the rate of all allergic reactions was significantly greater than placebo the comparison was to be considered NEGATIVE.

Secondary Analyses

The following analyses were also planned for the comparison between Ferrlecit and Placebo treatment:

- All adverse events (both SAEs and non-serious) using COSTART preferred term.
- Time from infusion to SAE both with and without investigator assessments of attribution for SAEs (not related, unlikely, probably related, possibly related, and unknown) using survival analysis, including Kaplan-Meier plots and both the log-rank and the Wilcoxon tests.
- Hypotensive reaction including the rate, the time from infusion until the occurrence of hypotension event, the severity of the event, and the investigator attribution.
- Anaphylaxis.
- Subgroup analysis by concomitant angiotensin converting enzyme inhibitor (ACE inhibitor) therapy. This analysis used the patient population consisting of those patients who received both Ferrlecit® and placebo infusions. The analysis used a logistic regression model including the factors of ACE inhibitor group (uses or does not use ACE inhibitor), Treatment group (Ferrlecit® or placebo), and the interaction of the two factors.
- Subgroup analysis by history of dextran sensitivity (yes or no). If the patient numbers were large enough, comparisons were to be made between the no prior dextran sensitivity group and the prior dextran sensitivity group for Outcome AEs, LAEs, anaphylaxis, and allergic adverse events.

Statistical significance was to be declared if the two sided p-value is < 0.05

Interim Analysis

The protocol provided that an interim analysis may be performed after 1,100 patients have completed study infusions with both Ferrlecit® and placebo. Only the CRO statistician and analysis programmer who prepares the interim summaries and analysis was to have access to the unblinded results. R&D Laboratories was to be provided unblinded safety summaries by treatment group only.

Sample Size Determination

The sample size for the study was determined assuming a control group outcome reaction rate of 2.78%, which is 2.47% + 0.31%, where 0.31% was the standard error of the 2.47% estimate. For Ferrlecit®, the outcome reaction rate was assumed to be no more than 1.60%. Using 80% power and a two-sided significance level of 0.05, it was determined, using the method of Makuch and Simon, that a total of 2409 completed patients would be required for the study. Assuming that 10% of the patients were to be discontinued or lost, a total of 2700 patients were to be included in the study. In addition, it was determined that with a study of 2,409 patients, Ferrlecit® could be shown to be significantly different from the iron dextran historical LAE control rate of 0.6%, if the LAE rate for Ferrlecit® was 0.16% or less. Furthermore, 2409 patients were determined to be sufficient to allow for the comparison between the Ferrlecit and placebo groups to detect a difference of 0.56% if the placebo allergy rate was approximately 1%.

3.2 Protocol Ammendments

There were two amendments to the protocol after the study started (August 19, 1999): (1) the first was on March 7, 2000, increased the hemoglobin level for entry from <12.5 gm/dL to <13.5 gm/dL at the request of several investigators who noted changing standards for treatment of iron deficiency anemia in the hemodialysis patient; and (2) the second was on March 16, 2000, (and finally adopted on June 12, 2000) amended to include the interim analysis in the study.

3.3 Study Interim Analysis Results

3.3.1 Disposition of Patients

In this interim analysis, 1106 hemodialysis patients were enrolled at 46 study centers and received at least one infusion (ITT population). Of these patients, 1089 received both Ferrlecit and placebo and were included in the per-protocol population. The following table summarizes the patient disposition in the study.

Table 5 Summary of Patient Disposition

Disposition	All Treatment Groups N=1106	
Number of Patients Enrolled	1106	
Intent-to-Treat Patients[a]	1106	
Number of Patients Discontinued after HD#2	17	
Number of Patients Discontinued by Treatment	8 (Ferrlecit® Only)	9 (Placebo Only)
Per-Protocol Population[b]	1089	
Per-Protocol Population by Treatment	1097 Ferrlecit®	1098 Placebo
Number of Patients Who Discontinued After HD#3 Before Completing the Study	0	
Number of Patients Who Completed the Study	1089	

[a] Patients who completed at least HD#2.
[b] Patient population for secondary analysis, patients who completed HD#2 and 3. Analyses for the per-protocol population were not performed for this interim report.
HD = Hemodialysis
Source: End-of-Text Table 10.2 and Table 1

Sponsor's table in NDA Vol. 38.5, IV.E.1.a), pp. 49
Note: Number of patients discontinued by treatment should be 7 for Ferrlecit and 10 for Placebo.

There were 17 (1.6%) patients who discontinued the study including 7 patients who received Ferrlecit only and 10 patients who received placebo only. Ten of the 17 (0.9%) patients discontinued the study prematurely in association with an adverse event after a single study drug administration (4 received Ferrlecit only; 6 received placebo only). Four were considered not related to study drug by investigator: 3 patients were hospitalized after the first study drug session (Ferrlecit: pneumonia and aggravated hypertension; Placebo: sepsis); 1 patient had non-serious event (Placebo: back pain, dizziness and insomnia). Six patients discontinued the study due to a related protocol event; 2 received Ferrlecit only (hypertension and chills) and 4 received placebo only [abdominal pain, allergic reaction (2), and sepsis]. The other seven patients withdrew for the following reasons: 4 withdrew consent without explanation; 2 were discovered to be in protocol violation intrastudy (steroid and intravenous antibiotic therapy, respectively); and, 1 was incarcerated intrastudy.

The following table presents reasons for discontinuation for all patients enrolled into this study.

Table 6 Summary of Reasons for Discontinuation

Patient Status	All Treatment Groups N=1106 n (%)
Completed Study	1089 (98.5)
Discontinued Study	17 (1.5)
Adverse Event(s)	10 (0.9)
Related Adverse Event	6 (0.6) (2 withdrew consent)
Unrelated Adverse Event	4 (0.4) (1 withdrew consent)
Protocol Violation	3 (0.3)
Withdrew Consent w/o explanation	4 (0.4)

Of the ten patients who discontinued prematurely after an adverse event, three experienced a serious unrelated intrastudy hospitalization; one had an unrelated non-serious adverse event and then withdrew consent; and six withdrew following a protocol event and then withdrew consent.
Data Source: Patient Data Listing End of Text Table 10.2 and Table 2

Sponsor's table in NDA Vol. 38.5, IV.E.1.a), pp. 50

The following table summarizes the reasons for discontinuation following Ferrlecit and Placebo administration.

Reasons for discontinuation following Ferrlecit and Placebo treatment

Reasons	Ferrlecit	Placebo
Adverse event	4	6
SAEs	3 (hypotension/facial swelling/nausea/vomiting, pneumonia, hypertension/weak/lightheaded/ near syncope)	2 (2 sepsis, 1 patient was febrile with abdominal tenderness on exam 2 days before placebo administration)
Non-SAEs	1 (chills)	4 (abdominal pain [patient had abdominal pain and LUQ tenderness 2 days before placebo administration], allergic reaction [patient reported gastrointestinal cramping 2 days later for previous placebo administration], mild nausea/vomiting/dizziness and headache, right lower leg/foot pain/lower back pain/dizziness/insomnia.
Withdrew consent w/o explanation	3	1
Protocol violation		3 (1 on steroid, 1 on antibiotics, 1 incarcerated)
Total	7	10

Reviewer's table

It should be noted that there were two patients withdrawn following placebo treatment who had adverse events (one SAE and one non-SAE) that started before placebo administration.

3.3.2 Protocol Deviations

Three in 1106 (0.3%) patients discontinued the study prematurely due to protocol violations. Of these, one patient was incarcerated, one patient received a concomitant medication (steroid) prohibited in the protocol, and one patient was undergoing antibiotic therapy for an acute infection (septicemia). All three patients discontinued the study after placebo administrations.

3.3.3 Demographic and Baseline Characteristics

The following table summarizes the demographic and baseline characteristics for all patients enrolled into this study. Of the 1106 patients enrolled into this study, 54.4% (602/1106) were male, 55.3% (612/1106) were Black, 21.4% (237/1106) were Caucasian, 20.0% (221/1106) were Hispanic, and the median age was 56 years. The ranges in height, weight, and blood pressure (both systolic and diastolic) were broad. The majority of the patients (93.5%; 1034/1106) had prior parenteral iron dextran exposure: 79.9% (884/1106) were exposed to InFeD®, 9.8% (108/1106) were exposed to Dexferrum®, and 3.8% (4211106) were exposed to both.

Table 7 Summary of Demographic and Baseline Characteristics (ITT Population)

Characteristic	All Treatment Groups N=1106
Age (years)	
N	1106
Mean (SD)	55.1 (15.15)
Median	56.0
Range (Min-Max)	19–92
Gender (n[%])	
N	1106
Male	602 (54.4)
Female	504 (45.6)
Childbearing Potential	91 (8.2)
Surgically Sterile	94 (8.5)
Post-menopausal	305 (27.6)
Other	14 (1.3)
Race (n[%])	
N	1106
Caucasian	237 (21.4)
Black	612 (55.3)
Asian/Oriental	24 (2.2)
Hispanic	221 (20.0)
Native American	1 (0.1)
Other	11 (1.0)
Height (cm)	
N	1100
Mean (SD)	168.20 (11.204)
Median	167.60
Range (Min-Max)	91.7–202
Missing	6
Weight (kg)	
N	1104
Mean (SD)	75.50 (20.125)
Median	72.00
Range (Min-Max)	34.5–175.0
Missing	2
Prior Parenteral Iron Exposure (n[%])	
N	1106
No	72 (6.5)
Yes	1034 (93.5)
InFeD®	884 (79.9)
Dexferrum®	108 (9.8)
InFeD® and Dexferrum®	42 (3.8)
Duration of Hemodialysis (minute)	
N	1106
Mean (SD)	218.0 (31.92)
Median	215.0
Range (Min-Max)	47–388
Systolic Blood Pressure (mmHg)	
N	1106
Mean (SD)	152.8 (24.86)
Median	152.0
Range (Min-Max)	77–255
Diastolic Blood Pressure (mmHg)	
N	1106
Mean (SD)	83.2 (15.66)
Median	82.0
Range (Min-Max)	29–176
Pulse (bpm)	
N	1099
Mean (SD)	79.9 (12.96)
Median	80.0
Range (Min-Max)	42–141
Missing	7

SD = Standard Deviation; Min = Minimum; Max = Maximum
Data Source: End-of Text Table 3.1.

Sponsor's table in NDA Vol. 38.5, IV.E.1.a), pp. 50-52

The following table summarizes prior sensitivity to iron dextran in those patients who had prior iron exposure. A total of 1034 of the 1106 (93.5%) patients enrolled in the study had prior parenteral iron exposure. Of these 1034 patients, 72 (7.0%) patients had prior sensitivity to at least one form of iron dextran. This represents 6.5% (72/1106) of total enrollment for this interim report.

Table 8 Summary of Patient Sensitivity to Prior Parenteral Iron Exposure (Prior Iron Dextran Exposed Population)

Iron Compound[a] Drug Sensitivity	All Treatment Groups N=1034 n (%)
Total Number of Patients[b]	72
InFeD®	
Mild	8 (0.8)
Drug Intolerance	35 (3.4)
Anaphylactoid	12 (1.2)
Dexferrum®	
Mild	2 (0.2)
Drug Intolerance	12 (1.2)
Anaphylactoid	7 (0.7)

[a] Not mutually exclusive. Some patients had prior exposure to both InFeD® and Dexferrum® and were counted more than once.
[b] Patients only counted once.
Data Source: End-of-Text Table 4.

Sponsor's table in NDA Vol. 38.5, IV.E.1.a), pp. 52

Concomitant Medications
Overall, the percentage of patients who received any concomitant ACE inhibitor therapy was 27.5% (304/1106).

3.3.4 Outcome Results

Data Sets Analyzed
The primary analysis group consisted of 1106 patients who had received at least one infusion (ITT population). A secondary per-protocol population consisted of 1089 patients who received two infusions.

Extent of Exposure
In this interim analysis of the single dose crossover study, 1097 patients were exposed to Ferrlecit (125 mg of elemental iron) and 1098 patients were exposed to placebo (10 mL saline). A total of 1089 patients were exposed to both Ferrlecit and placebo in the first hour of hemodialysis.

3.3.4.1 Primary endpoints-Protocol Events

1) Outcome (Drug Intolerance) Events

An outcome adverse event was one that would, in the view of the investigator, preclude further administration of Ferrlecit in the study protocol and was also named as drug

intolerance by the sponsor. The sponsor's table for the incidence of outcome adverse events by treatment is shown below:

Table 10 Incidence of All Outcome Events (ITT Population)

Body System[1] Preferred Term	All Treatment Groups N=1106 n (%)	
	Ferrlecit® N=1097	Placebo N=1098
Any Outcome Event[2]	8 (0.73)	2 (0.18)
Body as a Whole	5 (0.45)	1 (0.09)
Allergic Reaction	4 (0.36)	1 (0.09)
Anaphylactoid Reaction[3]	1 (0.09)	
Cardiovascular System	2 (0.18)	1 (0.09)
Hypotension	2 (0.18)	1 (0.09)
Digestive System	1 (0.09)	
Nausea	1 (0.09)	
Skin and Appendages	1 (0.09)	
Pruritus	1 (0.09)	

[1] Patients were counted only once within body system and preferred term. Only outcome adverse events were included.
[2] Indicates total number of patients with an outcome adverse event; no patient experienced two outcome events.
[3] This event was considered a life-threatening, outcome and suspected allergic event; however, tryptase levels fell indicating that the reaction was not due to clinically significant mast cell activation/degranulation.
Data Source: End-of-Text Table 17.1.1.

Sponsor's table in NDA Vol. 38.5, IV.E.1.a), pp. 58

Reviewer's Comments: *Based on examination of case report forms, one patient (028) had outcome adverse event but was not included in the table above. The patient developed pruritus 5 minutes after Ferrlecit administration and was treated with Benadryl 12.5 mg IV. The investigator considered the event to be moderate in intensity, probably related to study drug administration and required permanent cessation of drug treatment. The sponsor explained the missed case in the summary of submission but it was not added in the study results. This event should be considered as an outcome adverse event according to the definition in the study protocol. The incidence of outcome adverse events in the table above should be 0.82% (9/1097). This event was classified as an allergic reaction by the investigator and the rate of allergic reaction should be 0.46% (5/1097).*

Nine of 1097 (0.82%) patients each experienced one outcome event (drug intolerance) following Ferrlecit administration. Of the 9 outcome events, one was life-threatening event (anaphylactic/anaphylactoid reaction: flushing, sweating, nausea, vomiting, severe lower back pain, dyspnea and wheezing for 20 minutes), two were serious events (pruritus and hypotension), and the remaining six were non-serious events (nausea, chills, SOB/chest and back pain, rashes, flushing, and pruritus). These events would preclude further administration of Ferrlecit in the view of the investigator. Seven of these events were also classified as clinically suspected allergic adverse events.

Two of the 1098 (0.18%) patients each experienced one outcome event (drug intolerance) following placebo administration. One was also identified as a suspected allergic event (GI symptoms) but this event was not a confirmed allergic event. The other event was hypotension (BP decreased to 84/43 at 25 minutes after completion of placebo infusion and it was resolved after 100 mL normal saline infusion). None of events was identified as serious events.

The following table shows the sponsor's comparison in the incidence rate of outcome event between Ferrlecit from this interim analysis and iron dextran from 3 publications. The 95% confidence interval for Ferrlecit was compared to 68% of confidence interval of iron dextran.

Incidence of Outcome Adverse Event between Ferrlecit in the Current Study and Iron Dextran from 3 Publications

Outcome Adverse Event (Drug intolerance)	Iron Dextrans from 4 publications (n=2589)	Ferrlecit (n=1097)
Events	64	9*
Incidence rate	2.47%	0.82%
Sponsor's comparison	overall average rate ± standard deviation 2.16%-2.78%	95% confidence interval of rate: 0.38%-1.55%

*one new event was included. 95% CI was calculated by FDA Statistician (Dr. Wen-Jen Chen).
Reviewer's table

The result was identified as POSITIVE.

2) Life-Threatening Adverse Events

One (0.09%) patient experienced a life-threatening adverse event following Ferrlecit administration in this interim analysis. The patient experienced an anaphylactic reaction within 4 minutes of the start of the infusion (Diaphoretic, hypotension, dyspnea, wheezing, nausea, vomiting, severe lower back pain for 20 minutes) and was treated with subcutaneous epinephrine, intravenous benadryl, hydrocortisone and IV fluids. The patient stabilized within 20 minutes shortly after epinephrine administration. The patient had a high tryptase levels at baseline (11.7 ng/mL), which fell to 10.8 ng/mL one hour after onset of the reaction. This patient had history of anaphylaxis reaction to iron dextran in both forms (InFeD® and Dexferrum®), rash after penicillin and pruritis following cephalexin. The pre-injection level of tryptase in this patient is near the upper limit of normal. No patient experienced life-threatening events following placebo administration.

The following table is the sponsor's comparison of the incidence rate of life-threatening events between Ferrlecit in this interim analysis and iron dextran from 4 publications:

Incidence of Life-threatening Events between Ferrlecit in the Current Study and Iron Dextran from 4 Publications

Outcome Adverse Event	Iron Dextran (n=3768)	Ferrlecit (n=1097)
Events	23	1
Incidence rate	0.61%	0.09%
Sponsor's comparison	Overall average rate ± standard deviation: 0.48%-0.73%	95% confidence interval of rate: 0.00%-0.51%

Reviewer's table

Reviewer's Comments: *. The overall incidence rates of drug intolerance and life-threatening events for iron dextran were based on 4 publications. There were major differences among the 4 publications and between these 4 publications and current Ferrlecit study in study design, study population, study drug dose regimen, frequency of exposure, and outcome assessment (See this reviewer's comments in section 3.1.7 Historical Control of Iron Dextran from Publications, page 17-18).*

3) Suspected and Confirmed Allergic Adverse Events

The sponsor's table for all suspected allergic adverse events by treatment is shown below:

Table 12 Incidence of Suspected Allergic Events (ITT Population)

Body System[1] Preferred Term	All Treatment Groups N=1106 n (%)	
	Ferrlecit® N=1097	Placebo N=1098
Any Suspected Allergic Event[2]	8 (0.7)	4 (0.4)
Body as a Whole	6 (0.5)	3 (0.3)
Allergic Reaction	5 (0.5)	3 (0.3)
Anaphylactoid Reaction[3]	1 (0.1)	
Digestive System	1 (0.1)	
Nausea[4]	1 (0.1)	
Nervous System	1 (0.1)	
Dizziness[4]	1 (0.1)	
Skin and Appendages	1 (0.1)	1 (0.1)
Pruritus	1 (0.1)	
Rash		1 (0.1)

[1] Patients were counted only once within body system and preferred term. Only suspected allergic adverse events were included. A suspected allergic adverse event was defined as an event suspected by the investigator as an allergic event. Bias in selection may have been introduced by the approved package insert warnings with regard to allergic reactions as primary adverse reactions to Ferrlecit® notwithstanding that most reported allergic reactions related to gastrointestinal or non-allergic systemic complaints in this study.

[2] Indicates total number of patients with one or more suspected allergic adverse event.

[3] This event was considered a life-threatening, an outcome, and a suspected allergic event. However, tryptase levels fell indicating that the reaction was not likely due to clinically significant mast cell activation/degranulation.

[4] One patient had two suspected allergic adverse events (nausea and dizziness) simultaneously in response to Ferrlecit®; tryptase did not rise significantly and thus the event was confirmed as non-allergic.

Data Source: End-of-Text Table 17.1.3.

Sponsor's table in NDA Vol. 38.5, IV.E.1.a), pp. 60

Reviewer's Comments: *As this reviewer mentioned above in the section of "Outcome Adverse Event", one patient (028) had an outcome adverse event classified as an allergic event was not included in the sponsor's table above. The patient developed pruritus 5 minutes after Ferrlecit administration and was treated with Benadryl IV. The incidence of suspected allergic event in the table above should be 0.82% (9/1097). The rate of allergic reaction should be 0.54% (6/1097) and the rate of pruritus should be (0.18%).*

There were 9 (0.82%) patients who had suspected allergic events following Ferrlecit administration and 4 (0.36%) patients had suspected allergic events following placebo administration. One patient had two suspected allergic events (dizziness and nausea) following Ferrlecit that both were identified by the investigator as suspected allergic events. Allergic events following Ferrlecit were nausea/dry throat, pruritus (2), nausea/dizziness, flushing, chills, SOB/chest and back pain, and rashes. Suspected allergic events following placebo administration were abdominal pain/nausea, nausea/dizziness, flushing, and rashes.

Of the 9 patients with suspected allergic reactions following Ferrlecit administration, 8 had an event that occurred instantaneously on drug administration and one reported in the

following dialysis session (rashes). Of the 8 immediate events, pre- and post-tryptase levels were obtained for all patients and only one patient had a significant rise in tryptase (flushing immediately on start of Ferrlecit; drug withdrawn) that increased from 2.1 to 4.9 ng/mL.

Of the 4 patients with suspected allergic events following placebo, 2 patients reported the events (abdominal pain/nausea and rashes) in the following dialysis session (delayed) and 2 had an event that occurred instantaneously on drug administration. None of them had significant rise in tryptase value.

There was an overlap between suspected allergic events and outcome events. Two events following Ferrlecit administration were classified as suspected allergic events but they were not classified as outcome adverse events (i.e. did not preclude further drug administration). One had mild nausea/dry throat that was considered possibly related to study drug administration by the investigator. Another patient had mild nausea and dizziness during the Ferrlecit administration and Ferrlecit was discontinued. The investigator considered the event was mild and probably related to study drug administration but the event was not classified as requiring permanent discontinuation of drug treatment. Three events following placebo administration were classified as suspected allergic events but they were not classified as outcome events and those events were nausea/dizziness, flush and rash. The investigator considered all these events to be mild and possibly/probably related to study drug administration.

The following table shows the sponsor's comparison of 95% confidence interval of the incidence rate of suspected allergic events and confirmed allergic events (by tryptase) between Ferrlecit and placebo administration.

Incidence rate of suspected allergic events and confirmed allergic events following Ferrlecit and placebo administration

Events		Ferrlecit (n=1097)	Placebo (n=1098)
Suspected allergic events	Events Incidence 95% CI	9* 0.82% 0.38-1.55%	4 0.36% 0.10-0.93%
Confirmed allergic events (by tryptase)	Events Incidence 95% CI	1 0.09% 0.00-0.051%	0 0% 0.00-0.33%

*one new event was included. 95% CI was calculated by FDA Statistician (Dr. Wen-Jen Chen).
Reviewer's table

[redacted]. The result was identified as positive because there was an overlap of confidence interval.

Reviewer's Comments: [redacted]

Anaphylactic Allergic Events
An anaphylactic allergic adverse event was defined as a life-threatening adverse event with post-administration signs or symptoms of an anaphylactic reaction (bronchospasm, laryngeal edema, rash, pruritus, or urticaria) and with clinically-significant increase tryptase level in the study protocol. One patient experienced a life-threatening adverse event with sign or symptoms of an anaphylactic reaction following Ferrlecit administration but tryptase level was not significantly increased.

Non-Anaphylactic Allergic Events
A non-anaphylactic allergic adverse event was defined as an adverse event with postadministration signs or symptoms of an allergic reaction (rash, pruritus, cramps, abdominal or other acute spasmodic pain, nausea and vomiting) and with clinically significant increase in tryptase level. There was one patient who had a non-anaphylactic immediate type allergic event which was following Ferrlecit administration. This patient had a history of allergic reaction to InFeD® (iron dextran). The patient experienced pronounced facial flushing instantaneously after the start of study drug administration. No hypotension was noted. The event was not identified as serious. Tryptase increased from 2.1 ng/mL to 4.9 ng/mL.

Summary of All Life-Threatening, Outcome, and Suspected Allergic Adverse Events
A total of 16 patients (1.3%; 15/1106) in the study had a protocol-defined event (outcome, life-threatening, suspected allergic) including 11 following Ferrlecit (1.0%; 11/1097) and 5 following placebo (0.05%; 5/1098). Of the 4 patients with serious events identified as related, three followed Ferrlecit (0.3%; 3/1097) and one followed placebo (0.09%; 1/1098)(p=0.374).

A summary of all protocol events is attached in Appendix 2.

3.3.4.2 Secondary endpoints

1) Protocol Adverse Events by Prior Iron Dextran Sensitivity
A total of 1034 of the 1106 patients enrolled in the study had prior parenteral iron exposure. Seventy-two (7.0%) of the 1034 patients who had prior iron dextran exposure had a sensitivity to at least one form of iron dextran (Infed or Dexferrum). The protocol limited entry of dextran sensitive patients to no more than 10% per site to preclude enrichment with highly atopic patients and because the baseline published rate of dextran sensitivity is approximately 8%.

The following table shows the protocol events in patients with and without prior iron dextran sensitivity by treatment:

Protocol Events following Ferrlecit and Placebo Administration by Prior Iron Dextran Sensitivity

Protocol Events	Patients with prior iron dextran sensitivity (N=72)		Patients without prior iron dextran sensitivity (N=962)	
	Ferrlecit	Placebo	Ferrlecit	Placebo
Outcome AEs	2 (2.8%)	0	7 (0.7%)	2 (0.2%)
Life-threatening AEs	1 (1.4%)	0	0	0
Suspected allergic AEs	2 (2.8%)	1 (1.4%)	7 (0.7%)	3 (0.3%)
Confirmed allergic AEs	1 (1.4%)	0	0	0
Total	2 (2.8%)	1 (1.4%)	9 (0.9%)	4 (0.4%)

Reviewer's table

Patients with prior iron dextran sensitivity had approximately four time higher incidence of outcome AEs and suspected allergic AEs following Ferrlecit administration than those without prior iron dextran sensitivity. Both the patient with life-threatening AE and the patient with confirmed allergic AE following Ferrlecit administration had prior iron dextran sensitivity. The patient who experienced a life-threatening adverse event during the study had a previous severe anaphylactic reaction to dextran in both forms -InFeD® and Dexferrum®. Overall, the incidence of protocol events was 2.8% in patients with prior iron dextran sensitivity compared to 0.9% in patients without prior iron dextran sensitivity following Ferrlecit administration. Only one patient with suspected allergic event following placebo administration had prior iron dextran sensitivity and other 4 patients with outcome/suspected allergic events had no prior iron dextran sensitivity. The result suggests that about 3% of patients who have iron dextran sensitivity may have cross reaction with Ferrlecit for protocol events and 1% of patients who have no prior iron sensitivity may develop protocol events with Ferrlecit.

2) Protocol Adverse Events by Concomitant ACE Inhibitor Use

A total of 304 of the 1106 (27.5%) patients enrolled in the study received concomitant ACE inhibitor therapy. The following table shows the incidence of protocol events in patients with or without concomitant ACEi therapy by treatment:

Protocol Events following Ferrlecit and Placebo Administration by Concomitant ACE Inhibitor Use

Protocol Events	Patients with concomitant ACEi therapy (N=304)		Patients without concomitant ACEi therapy (N=802)	
	Ferrlecit	Placebo	Ferrlecit	Placebo
Outcome AEs	4 (1.3%)	0	5 (0.6%)	2 (0.2%)
Life-threatening AEs	0	0	1 (0.1%)	0
Suspected allergic AEs	4 (1.3%)	0	5 (0.6%)	4 (0.5%)
Confirmed allergic AEs	0	0	1 (0.1%)	0
Total	5 (1.6%)	0	6 (0.7%)	5 (0.6%)

Reviewer's table

Patients with concomitant ACEi therapy had double the incidence of outcome event, suspected allergic events, and total protocol events of those without concomitant ACEi therapy. However, neither the patient with life-threatening event nor the patient with confirmed allergic event was on ACEi therapy. It is worth noting that none of the five protocol events following placebo administration occurred in patients on ACEi. Since use

of ACEi was not randomized in the study, it is difficult to draw any conclusions from these results.

3) All Adverse Events

The following table summarizes all non-serious and serious adverse events that occurred during the study. The percentage of patients who experienced at least one adverse event was 18.0% (199/1106), of which 5.9% (65/1106) experienced an adverse event that was considered by the investigator to be related to study drug. Thirteen (1.2%; 13/1106) patients reported at least one serious adverse event during the study. Of these, four (0.4%; 4/1106) patients had a serious adverse event that was considered by the investigator to be related to study drug.

Table 25 Incidence of Non-Serious and Serious Adverse Events (ITT Population)

Type of Adverse Event	All Treatment Groups N=1106 n(%)		
	Ferrlecit® N=1097	Placebo N=1098	Total N=1106
Patients with Any Adverse Event[a]	123 (11.2)	103 (9.4)	199 (18.0)
Patients with Related Adverse Event[b]	45 (4.1)	30 (2.7)	65 (5.9)
Patients with Unrelated Adverse Event[b,c]			141 (12.7)
Patients with Any Serious Adverse Event[d]	8 (0.7)	5 (0.5)	13 (1.2)
Patients with Related Adverse Event[b]	4 (0.4)	1 (0.1)	4 (0.4)
Patients with Unrelated Adverse Event[b]	4 (0.4)	4 (0.4)	9 (0.8)

[1] Indicates total number of patients with one or more adverse event.
[2] Adverse events in relation to study drug are either related (possibly or probably) or unrelated (not related or unlikely); does not include the one event that was of unknown relationship to study drug.
[3] One patient who experienced an adverse event that was of unknown relationship to study drug was not included.
[4] Indicates total number of patients with one or more serious adverse event.
Data Source: End-of-Text Tables 17.1.7, 17.1.8, 17.2.3.6; Listing 10.1.

Sponsor's table in NDA Vol. 38.5, IV.E.1.a), pp. 78

A total of 199 (18.0%) patients experienced at least one adverse event during the course of the study. Of these patients, 123 (11.2%; 123/1097) had an event following Ferrlecit and 103 (9.4%; 103/1098) had an event following placebo administration. An analysis of the preferred term listing of all adverse events (Ferrlecit versus placebo) was done to assess whether any preferred term, individually, or by body system was found to occur statistically significantly more frequently among patients receiving Ferrlecit versus placebo using Fishers Exact Test. The only p-value for body systems with a value below 0.1 occurred for the overall digestive system in which 2.8% (31/1097) of patients on Ferrlecit had reactions and 1.7% (19/1098) of patients on placebo had reactions (p=0.088). The only p-value for a preferred term with a value less than 0.10 occurred for nausea which occurred in 1.2% (13/1097) of Ferrlecit patients and 0.8% (9/1098) of placebo patients (p=0.065). There was no statistically significant association with any body system or preferred term.

The percentage of patients who experienced at least one adverse event was 18.0% (199/1106), of which 5.9% (65/1106) experienced an adverse event that was considered by the investigator to be related to study drug. There were 45 adverse events that were deemed related to Ferrlecit (4.1%; 45/1097). There were 30 adverse events that were deemed related to placebo (2.7%; 30/1098).

Reviewer's Comments:

1)

2) *This study was a cross-over study with only 2-day washout period between Ferrlecit and placebo. The comparison was made between overall Ferrlecit and overall placebo in the same population.*

3) *Ferrlecit is recommended to use as repeated administrations for an average of total doses for a treatment session. The adverse events that collected from this single dose study may not be representative of adverse events occurring with repeated dose administration.*

4) Deaths, Serious Adverse Events, and Discontinuations

Deaths

One (0.1%; 1/1106) patient experienced three serious adverse events (subdural hematoma, pneumonia, and sepsis) and subsequently died after three weeks of hospitalization. The investigator considered all three events and the consequent death to be of severe intensity and unrelated to study drug administration. The first event (hospitalization for chronic subdural hematoma) occurred at the close of dialysis on the same day as placebo administration. The following is the patient narrative:

78 year-old African-American male with chronic renal failure on hemodialysis for greater than one year. He had a history of peripheral vascular disease (resulting in a right above the knee amputation and multiple decubital ulcers), hypertension, atrial fibrillation and diabetes. Ferrlecit was administered on beginning at 07:20. Placebo was administered on beginning at 07:27. On completion of Hemodialysis session #3, at 10:35, at which placebo was earlier administered, he was admitted to the hospital based on a change in mental status. A CT scan on was positive for a small right subacute or chronic subdural hematoma. On development of left-sided weakness, repeat CT was consistent with a chronic right convexity subdural hematoma. During hospitalization, the patient was noted to have perihilar pneumonia due to Staphylococcus aureus confirmed by chest x-ray and sputum cultures. The patient subsequently developed sepsis as the result of gram- positive cocci in his blood and died An autopsy o revealed severe calcified atherscleroses of the coronary arteries including occlusion of the left circumflex, left ventricular hypertrophy, moderate aortic stenosis, pyelonephritis, subdural hematoma, pericardial adhesions, multiple nodules on the left lobe of the thyroid, decubital ulcers and cerebral atrophy. The investigator considered all three events and subsequent death to be of severe intensity and unrelated to study drug (placebo).

Serious Adverse Events

A total of 13 patients (1.2% 13/1106) experienced a total of 15 serious adverse events; one patient experienced three serious events. Of the 13 patients, 4 had events that were also identified as related events (pruritus, hypotension, and anaphylactoid reaction

following Ferrlecit administration; sepsis with rigors after receiving only placebo administration). The three Ferrlecit-associated events were also identified as outcome events.

With regard to serious adverse events deemed unrelated, one patient died 19 days after placebo administration and had 3 sequential events, all deemed unrelated. Of the eight other patients with unrelated serious adverse events (nodal tachycardia [2 days after receiving Ferrlecit], pneumonia, hypertension, miscarriage [7 weeks after receiving both Ferrlecit and placebo], hypercalcemia, graft site bleeding, hip fracture, and sepsis), three discontinued the study (2 after Ferrlecit and 1 after placebo).

The following table summarizes the serious adverse events following Ferrlecit and placebo administration.

Table 26 Incidence of All Serious Adverse Events (ITT Population)

Body System[1] Preferred Term	All Treatment Groups N=1106 n (%)		
	Ferrlecit® N=1097	Placebo N=1098	Total N=1106
Any Serious Adverse Event[2]	8 (0.7)	5 (0.5)	13 (1.2)
Body as a Whole	1 (0.1)	3 (0.3)	4 (0.4)
Anaphylactoid Reaction		3 (0.3)	1 (0.1)
Sepsis	1 (0.1)		3 (0.3)
Cardiovascular System	4 (0.4)	0	4 (0.4)
Hemorrhage	1 (0.1)	0	1 (0.1)
Hypertension	1 (0.1)	0	1 (0.1)
Hypotension	1 (0.1)	0	1 (0.1)
Nodal Tachycardia	1 (0.1)	0	1 (0.1)
Metabolic and Nutritional Disorders	0	1 (0.1)	1 (0.1)
Hypercalcemia	0	1 (0.1)	1 (0.1)
Musculoskeletal System	0	1 (0.1)	1 (0.1)
Pathological Fracture	0	1 (0.1)	1 (0.1)
Nervous System	0	1 (0.1)	1 (0.1)
Subdural Hematoma	0	1 (0.1)	1 (0.1)
Respiratory System	1 (0.1)	1 (0.1)	2 (0.2)
Pneumonia	1 (0.1)	1 (0.1	2 (0.2)
Skin and Appendages	1 (0.1)	0	1 (0.1)
Pruritus	1 (0.1)	0	1 (0.1)
Urogenital System	1 (0.1)	0	1 (0.1)
Abortion	1 (0.1)	0	1 (0.1)

[1] Patients were counted only once within body system and preferred term. Only serious adverse events were included.
[2] Indicates total number of patients with one or more serious adverse event. One patient experienced three serious adverse events.
Data Source: End-of-Text Tables 17.1.7

Sponsor's table in NDA Vol. 38.5, IV.E.1.a), pp. 82

Discontinuations
There were 17 patients who did not complete both study drug administrations. Ten of the 17 (0.90%; 10/1106) patients discontinued the study prematurely in association with an adverse event after a single study drug administration (6 received placebo only; 4 Ferrlecit only). Three of the ten discontinued due to an unrelated intrastudy hospitalization after the first study drug session (pneumonia and aggravated hypertension following Ferrlecit, sepsis following placebo). One of the ten discontinued based on an unrelated non-serious event (back pain, dizziness and insomnia after placebo). Six of the ten discontinued based on a related protocol event. Of these six patients with protocol events, four received placebo only (abdominal pain, allergic reaction (2), sepsis) and two Ferrlecit only (hypotension and chills).

The other seven patients withdrew for the following reasons: 4 withdrew consent without explanation; 2 were discovered to be in protocol violation intrastudy (steroid and intravenous antibiotic therapy, respectively); and, 1 was incarcerated intrastudy.

5) Adverse Events of Special Interest

Hypotension Reaction
There were 40 patients who experienced hypotension and four patients who experienced flushing (vasodilatation). One (0.1%; 1/1098) patient who experienced both hypotension and flushing during or right after placebo administration.

An analysis of any hypotension in relationship to Ferrlecit or placebo administration was performed. Subcategories of all events, severe events, immediate events, related events, and serious events were also examined.

Table 23 – Incidence of Hypotension in Relation to Treatment Group

Event	Ferrlecit®	Placebo	p Value
Hypotensive Event	2.01% 22/1097	2.09% 23/1098	1.00[1]
Hypotensive Event (Serious)	0.09% 1/1097	0% 0/1098	0.500[1]
Hypotensive Event (Severe)	0.09% 1/1097	0% 0/1098	0.500[1]
Hypotensive Event (Not Severe)	1.91% 21/1097	2.00% 23/1098	0.879[1]
Hypotensive (Immediate)	0.09% 1/1097	0.09% 1/1098	1.00[1]
Hypotensive Event (Not Immediate)	1.91% 21/1097	2.00% 22/1098	1.00[1]
Hypotensive Event (Probably related, Possibly Related or Unknown)	0.82% 9/1097	0.73% 8/1098	0.814[1]
Hypotensive Event (Not Related or Unlikely)	1.19% 13/1097	1.37% 15/1098	0.850[1]

[1] Ferrlecit® versus placebo (based on Fisher's exact test).

Sponsor's table in NDA Vol. 38.5, IV.E.1.a), pp. 74

No relationship of Ferrlecit to hypotension, whether serious, severe, immediate, or by relationship versus placebo could be identified.

Gastrointestinal reaction:

A total of 13 (1.2%; 13/1106) patients experienced at least one combination of the following events on the same study day: nausea, vomiting, diarrhea, pain, and hypotension. The most common combination was nausea and vomiting (0.9%; 10/1106). At this point, this table remains blinded to therapy.

Table 24 Number of Patients Reporting At Least Two of the Following: Nausea, Vomiting, Diarrhea, Pain, and Hypotension (ITT Population)

Preferred Term[1]	All Treatment Groups N=1106 n (%)
Any Adverse Event[2]	13 (1.2)
Nausea and Vomiting	10 (0.9)
Nausea and Diarrhea	0
Nausea and Pain	4 (0.4)
Nausea and Hypotension	0
Vomiting and Diarrhea	0
Vomiting and Pain	1 (0.1)
Vomiting and Hypotension	0
Diarrhea and Pain	0
Diarrhea and Hypotension	0
Pain and Hypotension	0

[1] Only adverse events were included.
[2] Indicates total number of patients with at least two of nausea, vomiting, diarrhea, pain, and hypotension.
Data Source: End-of-Text Table 17.1.10.

Sponsor's table in NDA Vol. 38.5, IV.E.1.a), pp. 75

6) All Adverse Events and serious adverse events by Concomitant ACE Inhibitor Use

A total of 21.4% (65/304) of patients on concomitant ACE inhibitor therapy and 16.7% (134/802) of patients not on concomitant ACE inhibitor therapy experienced at least one adverse event. In patients receiving concomitant ACE inhibitor therapy, the most common adverse events, as reported by ≥2% of patients, were hypotension (4.6%; 14/304), nausea (2.6%; 8/304), and headache (2.0%; 6/304); the incidence of these events in patients not receiving concomitant ACE inhibitor therapy was lower. The following table shows adverse events in relation to concomitant ACE inhibitor therapy, as reported by ≥2% of patients.

Table 20 Incidence of Adverse Events in Relation to ACE Inhibitor Therapy, as Reported by ≥2% of Patients (ITT Population)

	All Treatment Groups N=1106 n (%)	
Body System[1] Preferred Term	**ACE I N=304**	**No ACE I N=802**
Any Adverse Event[2]	65 (21.4)	134 (16.7)
Body as a Whole		
Headache	6 (2.0)	9 (1.1)
Cardiovascular System		
Hypotension	14 (4.6)	26 (3.2)
Digestive System		
Nausea	8 (2.6)	12 (1.5)

[1] Patients were counted only once within body system and preferred term. Only adverse events were included.
[2] Indicates total number of patients with one or more adverse event.
ACE I = Angiotensin-Converting Enzyme Inhibitor
Data Source: End-of-Text Table 17.2.1.6.

Sponsor's table in NDA Vol. 38.5, IV.E.1.a), pp. 71

The following table presents all serious adverse events in relation to concomitant ACE inhibitor therapy.

Table 21 Incidence of All Serious Adverse Events in Relation to ACE Inhibitor Therapy (ITT Population)

Body System[1] Preferred Term	All Treatment Groups N=1106 n (%) ACE I N=304	No ACE I N=802
Any Serious Adverse Event[2]	5 (1.6)	8 (1.0)
Body as a Whole	0	4 (0.5)
Anaphylactoid Reaction	0	1 (0.1)
Sepsis	0	3 (0.4)
Cardiovascular System	2 (0.7)	2 (0.2)
Hemorrhage	0	1 (0.1)
Hypertension	1 (0.3)	0
Hypotension	1 (0.3)	0
Noda Tachycardia	0	1 (0.1)
Metabolic and Nutritional Disorders	0	1 (0.1)
Hypercalcemia	0	1 (0.1)
Musculoskeletal System	1 (0.3)	0
Pathological Fracture	1 (0.3)	0
Nervous System	0	1 (0.1)
Subdural Hematoma	0	1 (0.1)
Respiratory System	1 (0.3)	1 (0.1)
Pneumonia	1 (0.3)	1 (0.1)
Skin and Appendages	1 (0.3)	0
Pruritus	1 (0.3)	0
Urogenital System	0	1 (0.1)
Abortion	0	1 (0.1)

[1] Patients were counted only once within body system and preferred term. Only serious adverse events were included.
[2] Indicates total number of patients with one or more serious adverse event. One patient experienced three serious adverse events.
ACE I = Angiotensin-Converting Enzyme Inhibitor
Data Source: End-of-Text Patient List 10.1 and Patient Narratives.

Sponsor's table in NDA Vol. 38.5, IV.E.1.a), pp. 73

Five (1.6%; 5/1106) patients who received concomitant ACE inhibitor therapy and 8 patients (1.0%, 8/802) who did not receive ACE inhibitor experienced at least one serious adverse event during the course of the study. Of the 8 Ferrlecit-associated serious adverse events, 1.3% (4/304) occurred in patients on ACEi, and 0.50% (4/802) occurred in patients not on ACEi. Of the 7 serious adverse events associated with placebo, 0.3% (1/304) occurred in patients on ACEi and 0.7% (6/802) occurred in patients not on ACEi. Three serious events occurred in one patient not on concomitant ACEi therapy.

4. Post-marking Safety Review

4.1 Published literature

There have been no publications since the approval of Ferrlecit on February 19, 1999 other than the pivotal trial report submitted in the original NDA from the sponsor.

4.2 Spontaneous adverse events report system from manufacturer

The following table shows the frequency of adverse events associated with Ferrlecit reported to the sponsor from February 1999 to July 2000 from manufacturer:

AE Frequency Report for Ferrlecit (Feb. 1999-Jul. 2000)

Body System-Preferred Term	Total Number of AEs
BODY	
Abdominal Pain	10
Accidental Injury	3
Aggravation Reaction	1
Allergic Reaction	7
Anaphylactoid Reaction	1
Back Pain	11
Cellulitis	1
Chest Pain	16
Chills	7
Fever	1
Headache	7
Injection Site Inflammation	1
Injection Site Pain	1
Injection Site Reaction	9
Malaise	1
Overdose	10
Pain	6
Reaction Unevaluable	1
CV	
Atrial Fibrillation	1
Bradycardia	1
Heart Arrest	1
Hypotension	34
Pallor	1
Palpitation	1
Syncope	2
Tachycardia	5
DIG	
Colitis	1
Diarrhea	5
Dyspepsia	1
Fecal Incontinence	1
Flatulence	1
Gastrointestinal Hemorrhage	1
Nausea	17
Vomiting	10
MAN	
Cyanosis	1
Edema	9
MS	
Arthralgia	3
Leg Cramps	1
Myalgia	1
NER	
Acute Brain Syndrome	1
Agitation	1
Anxiety	4
Brain Edema	1

AE Frequency Report for Ferrlecit (Feb. 1999-Jul. 2000)
(Continued)

Body System-Preferred Term	Total Number of AEs
Cerebrovascular Accident	1
Coma	2
Convulsion	1
Dizziness	7
Hypertension	8
Hyperthesia	1
Insomnia	2
Nervousness	1
Paresthesia	2
Stupor	1
Tremor	1
Vasodilatation	9
RES	
Apnea	1
Asthma	1
Cough Increased	1
Dyspnea	13
Epistaxis	1
Laryngismus	1
SKIN	
Pruritus	21
Rash	4
Skin Discoloration	2
Sweating	4
Urticaria	8
SS	
Ear Disorder	1
Taste Perversion	2

Overall Unique AERs for Report = 114
Sponsor's table in NDA Vol. 40.1, D 5

Among the total 114 reports, 7 cases of allergic reactions and one case of anaphylactoid reaction were reported. The most reported events included hypotension (34 cases), pruritus (21 cases), nausea (17 cases), chest pain (16 cases), dyspnea (13 cases), back pain (11 cases), abdominal pain (10 cases), vomiting (10 cases), and overdose (10 cases). The severity of events was not specified. The sponsor indicated that one event was coded as "heart arrest" in the initial coding but it was not included in the current coding and in the report. According to report from MedWatch, a 52 year-old female patient developed hives on extremities after receiving 250mg Ferrlecit. Benadryl 50mg IV and hydrocortisone 125 mg IV were given. Hives resolved within 3 hours. The patient complained of being nauseated, then become unresponsive. The patient's eyes rolled back in her head and the patient became stiff; event lasted about one minute. The patient was given oxygen and normal saline and event resolved. The event was considered as serious adverse event. In the report, convulsion was coded as the first adverse event term.

4.3 Search from AERS

A search from AERS was conducted by this reviewer. A total of 86 adverse event reports have been found in AERS using Ferrlecit as the "suspect" drug on October 4, 2000. There were 2 deaths (1 in U.S. and 1 in foreign country), life-threatening events. A total of 9 allergic/anaphylactoid reactions were reported including 2 life-threatening event and serious events.

Deaths:
Two deaths were reported between Ferrlecit approval (February 18, 1999) and October 4, 2000. One patient (in U.S.) had cerebrovascular accident with brain edema after Ferrlecit infusion and subsequently died. The investigator considered the event was unlikely related to Ferrlecit administration. Another patient (in Spain) experienced a myocardial infarction during hemodialysis and developed massive hemolytic anemia, disseminated intravascular coagulation and acute pulmonary edema, and subsequently died. The exact cause of death was not specified. The patient received several medications including Ferrlecit during that period. The narratives of two deaths are attached in Appendix 3.

Life-threatening events:
There were 5 cases of life-threatening events reported during this period. Of these 5 patients, 2 received test dose only and 3 were overdosed. All events were consistent with hypersensitivity reactions. All 5 patients were female. Two patients had end-stage-renal disease as the underlying condition and one of them was indicated on chronic hemodialysis. The other 3 patients had general iron deficiency anemia as the underlying conditions. All 5 patients had been exposed to iron dextran previously. Three of these patients had prior hypersensitivity reactions to iron dextran. The summaries of 5 life-threatening events are attached in Appendix 4.

Allergic/anaphylactoid events:
There were 14 unduplicated reports using "allergic reaction" or "anaphylactoid reaction" as adverse event terms. Eight of these reactions were identified as serious adverse events. Two of them were life-threatening events. Symptoms/signs of allergic/anaphylactoid reactions included dyspnea, urticaria, pruritus, nausea/vomiting, chest pain, back pain, vasodilatation, hypotension, and convulsion. In many cases, events were reported that could have resulted from an allergic reaction (chest pain, back pain, nausea, vomiting, pruritus, rash/urticaria, convulsion) but the report did not include allergic reaction as the adverse event term.

5. Financial Disclosure
The sponsor has provided a certification that no financial arrangements with an investigator, who conducted clinical study FER9803, have been made where outcome affects compensations (Form FDA 3454).

6. Reviewer's Discussion

6.1 Discussion of Study FER9803 Interim Analysis
FER9803 is a multicenter, randomized, double-blinded, crossover, single dose, and placebo-controlled study of the safety of Ferrlecit® in hemodialysis patients with iron deficiency anemia. Ferrlecit 125 mg was administered by undiluted slow injection over 10 minutes (12.5 mg/min). No test dose was used. The primary safety endpoints were life-threatening events, drug intolerance events and allergic events. This study is ongoing currently and is expected to enroll 2700 hemodialysis patients. This interim analysis report contains results from 1106 hemodialysis patients with iron deficiency anemia.

The incidence of life-threatening events and drug intolerance events of Ferrlecit in this study were compared to iron dextran in historical control identified from a meta-analysis of 4 publications.

There were major differences in study design, study population, study drug regimen, frequency of exposure, and outcome assessment between 4 published iron dextran studies and current Ferrlecit study. The major deficiencies in iron dextran historical controls are listed below:

1) Study design: Two publications (Fishbane and Faich) were based on retrospective review (Fishbane was based on medical records; Faich was based on medication review).
2) Study population: Two publications (Hamstra and Feridex) were studies conducted in a different study population (Hamstra was in patients with general iron deficiency anemia; Feridex was in patients with suspected liver damage undergoing MRI). Patients' age and gender were different between the four publications (Hamstra study had younger patients and more women).
3) Study drug: Only 2 publications indicated that current iron dextran preparations were used in the studies (INFed in Fishbane and unspecified iron dextran in Faich). Imferon (withdrawn from market in 1991) was the study drug in Hamstra and Feridex (a different type of iron dextran as a contrast agent) was a study drug in another publication. The dosage was different between drugs in the 4 publications. Repeated dose regimens were indicated in 2 publications (Hamstra and Fishbane).
4) Outcome assessment: Different criteria for life-threatening events and drug intolerance events were used in 4 publications. Hamstra was conducted 30 years ago and the events leading to drug intolerance were significantly different from other studies. Life-threatening events in Fishbane study and drug intolerance in three publications (except Feridex) were collected from repeated exposure.
5) No protocols, data listings, or study reports were provided for these 4 publications.

These major differences between the published iron dextran studies and the current Ferrlecit study may bring significant uncertainty to the conclusion of treatment comparison. The comparison between repeated dose exposure of iron dextran in publications and single dose exposure of Ferrlecit in the current FER9803 study may introduce significant bias in favor of Ferrlecit. Therefore, this historically controlled study could not be considered as an adequate and well-controlled study.

In the interim analysis report of current Ferrlecit study FER9803, one life-threatening event (0.09%) due to hypersensitivity reaction was found following the first single dose of Ferrlecit administration in 1097 hemodialysis patients with iron deficiency anemia. Of 1097 patients, there were 9 patients (0.82%) who had an adverse event, in the view of the investigator, precluding further administration (drug intolerance) including one life-threatening event, 6 suspected allergic events, and two other events. A total of 9 suspected allergic events (0.82%) were found in 1097 patients following Ferrlecit first dose administration. There were no life-threatening event but 2 drug intolerance events (one reported GI symptoms 2 days later and one had hypotension following

administration during dialysis), and 4 suspected allergic events (nausea/dizziness, flushing, GI symptom [reported 2 days later] and rash [reported later]; all were mild in intensity) following placebo (normal saline) administration.

The Ferrlecit study FER9803 is limited by absence of concurrent active-treatment control, single dose exposure and short (only 2 days) washout period between Ferrlecit and placebo treatment period. These limitations give no incentive to identify adverse events in the study (placebo equivalent safety trial); therefore, the incidence of safety endpoints could be underestimated. For life-threatening events, examination of intervention (medications such as epinephrine, Solu-Medrol) used during the study could provide some certainty for the event. Only one patient (the one identified case with life-threatening event) received epinephrine during the study. For drug intolerance events, the incidence rate could be underestimated because of the single dose planned and subjective criteria used. The investigator in this study may feel less pressured to identify these events because no repeated dose was scheduled for their study patients. This may bring bias in favor of Ferrlecit for drug intolerance events. For allergic events, the incidence rate may be underestimate due to single dose exposure. Some patients may experience allergic reactions on repeated dose without reaction to the first dose.

In FER9803, Ferrlecit was administered at dose of 125 mg of elemental iron given by slow injection over 10 minutes without a test dose in 1097 hemodialysis patients. It appears that these patients tolerated this administration well.

A total of 1034 of the 1106 patients enrolled in the study FER9803 had had prior parenteral iron exposure. Seventy-two (7.0%) of the 1034 patients who had prior iron dextran exposure had a sensitivity to at least one form of iron dextran (INFed or Dexferrum). The patient who experienced a life-threatening adverse event during the study had a previous severe anaphylactic reaction to dextran in both form -INFed® and Dexferrum®. The incidence of both drug intolerance and suspected allergic events were 2.8% in patients with prior iron dextran sensitivity compared to [redacted] in patients without prior iron dextran sensitivity following first dose Ferrlecit administration. The result suggests that about 3% of patients who have iron dextran sensitivity may have cross reaction with Ferrlecit for drug intolerance and suspected allergic events and 1% of patients who have no prior iron sensitivity may develop these events with Ferrlecit. The patient with confirmed allergic AE following Ferrlecit administration also had prior iron dextran sensitivity.

A total of 304 of the 1106 (27.5%) patients enrolled in the study received concomitant ACE inhibitor therapy. The incidence of either drug intolerance or suspected allergic events was [redacted] in patients with concomitant ACEi use compared to [redacted] in patients without concomitant ACEi use following first dose Ferrlecit administration. The results suggest that there may be an interaction between Ferrlecit and ACEi and the risk of protocol events may be doubled with concomitant ACEi therapy. However, neither the patient with life-threatening event nor the patient with confirmed allergic event was on ACEi therapy.

6.2 Discussion of Sponsor's Proposed Labeling Changes

The sponsor has submitted the interim analysis results of Study FER9803 to request the following changes in labeling:

1). Warnings

(2) Flushing and hypotension reactions associated with rapid drug administration.

2). Clinical Studies

(1

(2

3). Adverse Reactions

Deletion . Addition of adverse events following Ferrlecit and placebo based on Study FER9803. Addition of the most commonly-occurring adverse reactions based on study FER9803 interim analysis.

4). Dosage and Administration

Deletion of test dose recommendation and addition of undiluted slow IV push at a rate of up to 12.5 mg/min as an alternative drug dosing regimen.

Hypersensitivity reactions

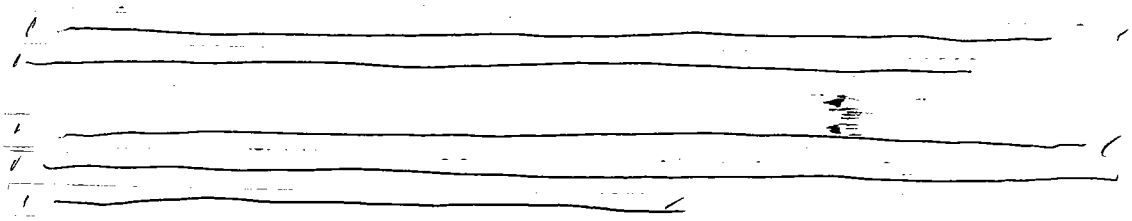
In 21 CFR 201.57 (g)(3), it states "the "Warnings" section of the labeling or, if appropriate, the "Contraindications" section of the labeling shall identify any potentially fatal adverse reaction."

In the submitted FER9803 study interim report, one case of life-threatening event was reported following a single dose Ferrlecit administration. Although the incidence of life-threatening events was low in study FER9803, the limitations of the study should be considered. In post-marketing spontaneous adverse event reports, life-threatening events due to hypersensitivity reactions were reported between February 18, 1999 (approval date) and October 5, 2000. This reviewer recommends that the fatal hypersensitivity reactions should be addressed in the warning section in the labeling to provide major safety information to the physician.

Flushing and hypotension reactions

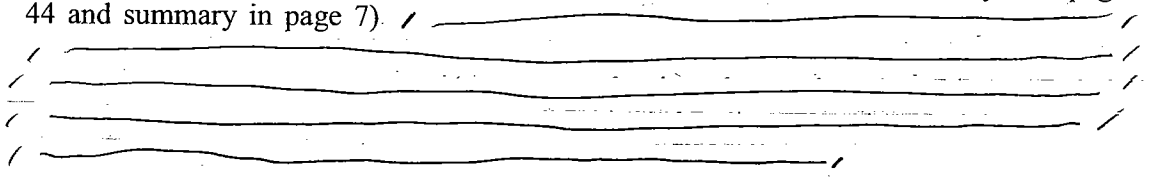
In current warning section, flushing and hypotension reactions associated with rapid drug administration were included. From literature report (Zanen, Nephrol Dial Transplant 1996; 11:820-824), two patients developed symptoms consisted of nausea, facial

reddening and hypotension after administrated Ferrlecit 62.5-125 mg of elemental iron during the final 30 minutes of dialysis. Both these patients had a calculated transferrin saturation of above 100% at the time of symptoms. The author suspected that patients' symptoms were caused by ionized 'free' iron due to oversaturation of transferrin by rapid infusion. However, this causal relationship was not established in the author's further study. In study FER9803 interim report, no event of serious flush and hypotension reactions has been reported following a single dose Ferrlecit that administered by slow injection over 10 minutes. However, there have been 2 additional cases reported from post-marketing spontaneous report system in United States. Therefore, this reviewer recommends flushing and hypotension reactions may be removed from the Warnings section but it should be addressed in Precautions section in current labeling.

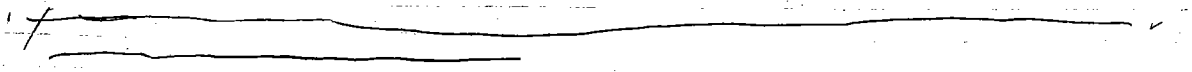


FER9803 is a multicenter, randomized, double-blinded, crossover, single dose, placebo-controlled study of the safety of Ferrlecit® in hemodialysis patients with iron deficiency anemia. The primary safety endpoints were life-threatening events, drug intolerance events and allergic events. The incidence of life-threatening events and drug intolerance events of Ferrlecit in this study were compared to iron dextran in historical control identified from a meta-analysis of 4 publications.

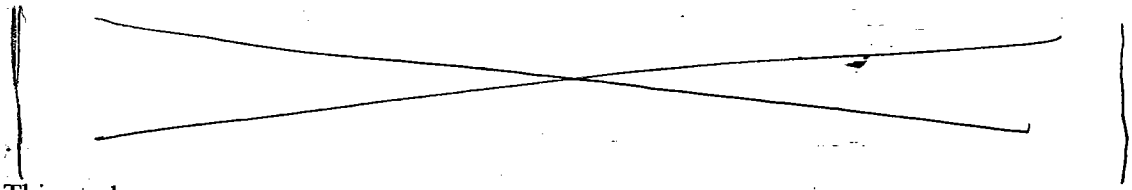
There were major differences in study design, study population, study drug regimen, frequency of exposure, and outcome assessment between 4 published iron dextran studies and current Ferrlecit study. The major deficiencies in iron dextran historical controls are listed in previous sections (See 6.1 Discussion of study FER9803 interim analysis in page 44 and summary in page 7).



FER9803 is a single dose study and the adverse events collected from study FER9803 is insufficiently informative for the intended repeated treatment for total 8 sessions for up to 1 gram of elemental iron recommended in current labeling. However, the study could provide some information on life-threatening events and allergic event for the first single dose Ferrlecit administration.



. FER9803 is a single dose, cross-over study of Ferrlecit and placebo with only two-day washout period.

1) 

2) This study was a cross-over study with only 2-day washout period between Ferrlecit and placebo.

3) Ferrlecit is recommended to use as repeated administrations for an average of total doses for a treatment session in the current labeling.

Changes in Adverse Reactions section

The sponsor requested to delete , to add comparison of all adverse events between single dose Ferrlecit and placebo administration, and to add common adverse reactions for Ferrlecit based on single dose administration.

Life-threatening hypersensitivity reactions have been reported in the study FER9803 (one case) and from post-marketing spontaneous report system (5 cases) in United States since its approval in February 1999. This important safety information should be presented in Adverse Reactions section, as well as in Warnings section. Flushing and hypotension reactions associated with rapid administration could be presented in precautions section.

As mentioned above, the comparison of all adverse events between Ferlecit and placebo in study FER9803 is inappropriate because of a short washout period (2 days). Common adverse events for Ferrlecit should not be based on a single dose administration from study FER9803 because Ferrlecit is recommended to use as repeated administrations for an average of 8 total doses for a treatment session in the current labeling.

Deletion of test dose recommendation and addition of undiluted slow IV push at a rate of up to 12.5 mg/min as an alternative doing regimen.

In study FER9803, Ferrlecit was administered at dose of 125 mg of elemental iron given by slow injection over 10 minutes without a test dose in 1097 hemodialysis patients. It appears that these patients tolerated this administration well. This reviewer concurs with the above changes in Dosages and Administrations section.

7. Conclusions and Recommendations

1).

(1) one life-threatening event due to hypersensitivity reaction was reported based on study FER9803 interim analysis, and (2) five life-threatening events due to hypersensitivity reactions have been reported from post-marketing spontaneous reports in United States.

2).

(1) There were major differences in study population, study design, study drug regimen, and outcome assessment between the published iron dextran studies and current Ferrlecit study

(2) Comparison of safety results between single dose drug exposure in the current Ferrlecit study to repeat dose drug exposure in the published iron dextran studies

(3)

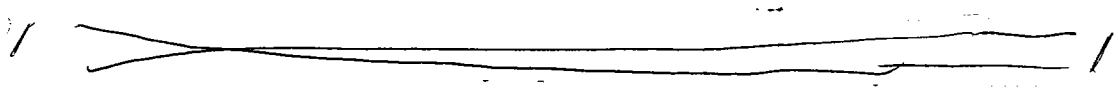
3).

(1) Incidence rates of events with both treatments (Ferrlecit and placebo) were low in study FER9803.

(2) The short washout period (2 days) in study FER9803 makes the comparison of adverse events between Ferrlecit and placebo inappropriate

(3) Ferrlecit is labeled for repeat dosing.

(4)



4). The request to delete test dose recommendation in Dosage and Administration section should be approved.

5). The request to add an alternative method of administration by slow injection over 10 minutes should be approved.

6). The request to remove flushing and hypotension reactions from the Warnings section in labeling should be approved (with recommendation of these reactions being included in Precautions section).

Min Lu, M.D., M.P.H.

cc:
NDA 20-955/SE8-003
HFD-180/Division file
HFD-180/L Talarico
HFD-180/K Robie-Suh
HFD-180/M Lu
HFD-180/B Strongin
HFD-180/J Choudary
HFD-720/T Permutt
HFD-180/L Zhou
HFD-180 S Doddapaneni

12/21/2000

Appendix 1. Summary of all protocol events

Table 15 Summary of All Life-Threatening, Outcome, and Suspected Allergic Adverse Events (ITT Population)

Patient ID	Preferred Term	LAE	Outcome	Suspected Allergic	Non-Allergic	Confirmed Allergic	Onset Time	Severity
-027 Ferrlecit®	Allergic Reaction (nausea, unease, dry throat)			X	X		Immediate	Mild
-078 Placebo	Allergic Reaction (abdominal cramps, diarrhea, nausea, itching, and flushing)		X	X			Delayed	Moderate
005 Ferrlecit®	Nausea		X				Instantaneous	Mild
-002 Ferrlecit®	Pruritus		X	X	X		Immediate	Moderate
-060 Ferrlecit®	Hypotension		X				Immediate	Severe
-005 Placebo	Allergic Reaction (nausea, dizziness, headache, and vomiting)			X	X		Instantaneous	Mild
-021 Ferrlecit®	Dizziness			X	X		Instantaneous	Mild
021 Ferrlecit®	Nausea			X	X		Instantaneous	Mild
-025 Placebo	Allergic Reaction (flushing and malaise)			X	X		Immediate	Mild
010 Ferrlecit®	Allergic Reaction (pronounced facial flushing)		X	X		X	Instantaneous	Severe
017 Ferrlecit®	Allergic Reaction (chills)		X	X	X		Immediate	Mild
016 Ferrlecit®	Anaphylactoid Reaction (flushing, sweating, nausea, vomiting, severe lower back pain, dyspnea and wheezing)	X	X	X	X		Immediate	Severe
003 Placebo	Hypotension		X				Immediate	Moderate
028 Placebo	Rash			X			Delayed	Mild
048 Ferrlecit®	Allergic Reaction (dyspnea and chest pain)		X	X	X		Instantaneous	Moderate
002 Ferrlecit®	Allergic Reaction (rash)		X	X			Delayed	Mild

Data Source: Listing 10.1; Patient Summary and Narratives at Tab IV.E.1.a.v.

Sponsor's table in NDA Vol. 38.5, IV.E.1.a), pp. 64

Appendix 2: Narrative of two deaths from post-marketing reports

Case #1 (in U.S.):

74-year old female Caucasian patient with end-stage renal disease, hypertension, severe peripheral vascular disease (status-post bilateral lower extremity bypass surgery), high cholesterol with bilateral carotid plaques and atherosclerosis, and a history of morbid obesity (lost weight over the past year to approximately 180 pounds), initiated hemodialysis in [redacted]. The patient was hospitalized in [redacted] (unknown admitting diagnosis), and was treated with Vancomycin, Gentamicin and Ancef (cefazolin). Upon discharge, she was referred to nephrologist (reporter) for follow-up and was started on Fortaz (ceftazidime). A few days later, the patient broke out in severe rash presumed to be related to Fortaz. The rash healed 2 weeks after Fortaz was discontinued. [redacted] INFed (iron dextran) was initiated for iron deficiency anemia. Patient received a test dose and 2 full doses (unknown doses) of INFed; then a rash similar to the previous episode developed. The rash eventually healed after 2 weeks. Patient then underwent vascular access surgery during which she bled, and the anemia worsened. [redacted], Ferrlecit was initiated and patient received a test dose (25 mg/100 ml normal saline) iv over 1 hour. The test dose was well tolerated. On [redacted] patient received the first full dose of Ferrlecit (8 ml/100 ml NS) iv over 1 hour during a dialysis session. Approximately 0.5 hour after the infusion was completed, facial dropping, progressive drowsiness and inability to move left side of body were noted. Then rapidly over the next 20 minutes, deep coma evolved. Prior to the onset of events, her blood pressure (BP) was 140/100 and heart rate (HR) was 70. After the onset of events, her BP was 200-210/90-100 with bradycardia (HR <35). Patient then became apneic and treatment with oxygen, first by nasal cannula then by facial mask was initiated. Patient was subsequently intubated, and was transported to the critical care unit of the hospital. She was also treated with Dilantin 1050 mg iv. A CT scan performed on 01Nov showed cerebrovascular accident (CVA) with brain edema, but no bleeding. Brain herniation was diagnosed based on clinical presentation. Patient was not hypotensive throughout the episode. The following day [redacted] while undergoing institutional brain death protocol, extensive right-sided ischemic CVA accompanied by brain edema was diagnosed. The patient was declared brain dead. She expired early in the morning of [redacted]. The primary cause of death was CVA. An autopsy was not performed. The reporter stated that the event has not been previously described in patients who received Ferrlecit; therefore, it is unlikely related to Ferrlecit. The reporter added that no additional information is forthcoming because the hospital would not release the patient's medical record.

Case #2 (in Spain):

63-year-old male patient with diabetes type II of long term evolution, ateromatosis and chronic renal insufficiency was treated with enoxaparin intravenous 40 mg (not specified if it's the daily dose) from [redacted]. The therapeutic indication was not provided. The patient was under hemodialysis since one year ago. During the last hemodialysis session, the patient was receiving Ticlopidin 250mg daily. In [redacted] (exact dates unknown): the patient underwent his hemodialysis session, during which he experienced a myocardial infarction. He was hospitalized and taken to the intensive care unit. He was found to have massive hemolytic anemia. He developed disseminated intravascular coagulation, acute pulmonary edema and subsequently died. The exact cause of death is not specified. The patient received enoxaparin at the beginning of each dialysis and Ferrlecit (unknown dose and regimen) and Neorecormon at the end. The reporter considers enoxaparin, ticlodipin, epoetin and ferrlecit as suspect drugs. No further information was provided.

Appendix 3. Life-threatening events reported by post-marketing spontaneous report system (between 2/19/1999 and 10/5/2000)

	Ferrlecit received	Underlying conditions	Adverse reactions
55 yrs, F	483 mg over 4 hours (500 mg over 4 hours was scheduled)	Iron-deficiency anemia, Crohn's disease, Prior exposure to iron dextran without adverse reaction.	Close to the completion of the infusion, patient complained of burning hands and swelling. Benadryl 25 mg IVP was administered. After a 20 minute rest, patient complained of chest pain with inspiration, dizziness, shortness of breath, and nausea. Head of bed was lowered and O2 started. BP was 59/32. Patient vomited and was incontinent of stool. Solu-Medrol 40 mg IVP was given and patient's symptoms subsided. No adverse events occurred on test dose.
35 yrs, F	389 mg over 1.17 hours (1 gm over 3 hours was scheduled)	Iron-deficiency anemia, History of allergic reaction to iron dextran	Patient was premedicated with ranitidine 150mg po -13 and 1 hrs and decadron 20mg po -13 and –1 hrs, and diphenhydramine 50mg po before a 25mg test dose of Ferrlecit. No adverse event occurred on test dose. About 1 hour and 15 minutes into the infusion, the patient developed hives, numbness of upper and lower extremities and pain and tightness in the chest and back. Diphenhydramine 50mg po and methylprednisone 40mg iv were administered. Within 10 minutes symptoms subsided and the patient became more alert.
27 yrs, F	25 mg test dose	End-stage-renal disease on hemodialysis, history of allergic reaction to iron dextran	Within minutes of initiation of the test dose, patient developed chest tightness and stated that she felt like her throat was closing up. Redness was also noted across her chest, face and arms. the infusion was discontinued, and patient was treated with oxygen at 4 L/min, intravenous bolus of normal saline (300 ml) , benadryl 50 mg iv, solu-cortef 250 mg iv. The event resolved. The reporter stated that patient had experienced similar events following treatment with InFed (iron dextran) in the past.
41 yrs, F	150 mg over 20 minutes (1.8 gm over 4 hours was scheduled)	Iron-deficiency anemia, prior exposure to iron dextran without adverse reaction	Approximately twenty minutes into the infusion, patient developed edema of upper extremities with itching, hypotension, shortness of breath, wheezing, intermittent abdominal pain, nausea, vomiting, back pain and diarrhea. The infusion was discontinued. Patient was treated with Benadryl 25 mg iv and solucortef or hydrocortisone 250 mg iv, and was taken to the emergency room. A CT scan of the abdomen revealed no acute process. Patient was hospitalized and was discharged the same day.
41 yrs, F	Unknown amount of test dose (25 mg)	End-stage renal disease and iron-deficiency anemia. History of anaphylaxis to iron dextran (INFeD). Patient was desensitized to INFeD successfully.	After a small amount of test dose given, patient developed generalized itch, shortness of breath, tightness in chest, and sensation of throat swelling. Treatment was stopped and she was treated with H1/H2 antihistamines (unspecified) and Solumedrol. Events resolved after treatment.

Reviewer's table

19 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 20-955
S003

/s/

Min Lu
1/30/01 11:24:59 AM
MEDICAL OFFICER

Kathy Robie-Suh
1/31/01 05:42:01 PM
MEDICAL OFFICER

Lilia Talarico
2/1/01 06:00:56 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: January 31, 2001

From: Kathy M. Robie-Suh, M.D., Ph.D.
Medical Team Leader, Hematology, HFD-180

Subject: NDA 20-955/S-003, submitted 10/5/2000
Ferrlecit (sodium ferric gluconate complex in sucrose injection)

To: Director, Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Ferrlecit is a parenteral iron preparation approved for marketing in the U.S. on February 18, 1999 for treatment of iron deficiency in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy. Ferrlecit has been marketed in a number of European countries since 1959.

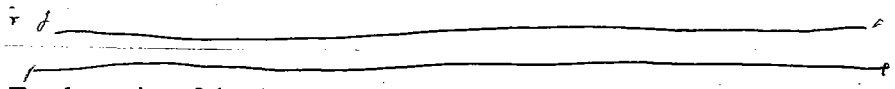
At the time of U.S. approval Ferrlecit professional labeling was required to carry the boxed warning associated with the administration of parenteral iron preparations since anaphylactic reactions have occurred with Ferrlecit and reporting compliance of all events had not been established and because there in general was a limited amount of safety information on Ferrlecit available.

The sponsor agreed to a number of Phase IV commitments, including:

- Conduct a study to provide additional safety data (e.g., incidence of allergic or anaphylactic reactions, cross-reactivity with other parenteral iron preparations), and
- Conduct a study to evaluate the possibly increased risk of allergic/anaphylactic reactions in patients receiving angiotensin converting enzyme inhibitor therapy and Ferrlecit concurrently.

In their December 30, 1998 submission to the NDA the sponsor provided Protocols FER9803 and FER9806 to address these commitments and these protocols were judged to be adequate in design to address the safety concerns expressed in the request for these two Phase IV commitments. The Division also commented that for Study FER9803, "Interpretation of the comparisons of Ferrlecit to historical iron dextran adverse events rates proposed as the primary statistical analyses is dependent on support provided for the historical rate figures."

In the current submission the sponsor presents an interim analysis of Study FER9803 and updated safety information on Ferrlecit to support a major rewrite of the the Ferrlecit labeling. The specific substantive clinical labeling changes being proposed include:

1. 
2. 
3. Total rewrite of the ADVERSE EVENTS section, based on FER9803 results including comparison to placebo .
4. Deletion of the requirement for a test dose of Ferrlecit from the DOSAGE AND ADMINISTRATION section.
5. Addition of a new dosing regimen to the DOSAGE AND ADMINISTRATION section.

Also, changes to the DESCRIPTION and CLINICAL PHARMACOLOGY sections of the labeling are proposed.

The supporting information provided in this submission includes data on 2025 patients who received Ferrlecit in Study FER9803 (interim study report submitted), an additional 283 patients in publications and 159 patients from other North American studies. Also, material submitted in support of the changes to the CLINICAL PHARMACOLOGY section include study report for single-dose pharmacokinetic Study FER9801 in 14 healthy iron-deficient adult subjects.

Information supporting the proposed changes to the following sections has been reviewed by the medical reviewer: WARNINGS; CLINICAL TRIALS; ADVERSE EVENTS; DOSAGE AND ADMINISTRATION. The proposed changes for the DESCRIPTION section and the CLINICAL PHARMACOLOGY section of the labeling are being addressed by FDA Chemistry and FDA Biopharmaceutics, respectively.

The current Ferrlecit labeling (package insert) is attached to this review as Appendix A. The proposed changes are discussed below.

Summary and Interim Results for Study FER9803:
Study FER9803 was planned as a post-marketing safety study being done by the sponsor as part of a Phase 4 agreement to collect additional safety information on Ferrlecit. This study is ongoing but an interim analysis report (planned) is submitted in this application and constitutes the major support cited for the proposed clinical changes.

Study FER9803 is a randomized, double-blind, single-dose, cross-over study of Ferrlecit versus placebo in up to 2700 chronic hemodialysis patients with iron deficiency anemia on erythropoietin. The study involves 4 successive dialysis sessions: screening, treatment 1, treatment 2, and follow-up. Patients receive in random order at two successive dialysis sessions Ferrlecit [125mg (10ml)] or placebo [(10ml of saline containing 9 mg/ml benzyl alcohol)] each administered by slow injection over 10 minutes via the venous return line. No test dose is given. After preparation of study drug syringes by unblinded personnel, blinding is achieved by covering the syringes "with appropriate materials". Patient signs and symptoms during the hemodialysis session are recorded before during and after study drug administration. Patients without serious

problems in Study FER9803 continue into the open-label, repeat dose (10 hemodialysis sessions) Ferrlecit study FER9806. The primary study aims for FER9803 are:
(1) To compare Ferrlecit and placebo with regards to incidence of: Outcome Adverse Events (OAEs); Life-Threatening Adverse Events (LAEs); and all allergic reactions.
(2) To compare Ferrlecit and an iron dextran historical control with regards to incidence of: Outcome Adverse Events (OAEs); Life-Threatening Adverse Events (LAEs); and
(3) To assess the safety of administration of Ferrlecit at an injection rate of 12.5mg/min.

Outcome Adverse Events (OAEs) are defined as:

- Life-Threatening Adverse Events (defined as below); or
- another immediate reaction (other than hypotension) that requires permanent cessation of drug therapy; or
- recurrent or persistent hypotension after study drug administration which would preclude future therapeutic administration of the drug product; or
- a delayed reaction reported at the following hemodialysis session that is possibly or probably related to drug administration and that is sufficient to preclude future therapeutic administration of the drug product.

Life-Threatening Adverse Events (LAEs) are defined as:

- any immediate hypotensive reaction following drug or placebo administration which requires the institution of resuscitative measures which are not immediately (<10 minutes) responsive to protocol prescribed interventions [i.e., "...usual measures undertaken to manage hypotension in a dialysis setting should be undertaken, such as placement of the patient in a head-down position or cessation or slowing of ultrafiltration, or the injection of Ferrlecit may be temporarily stopped."] and thus requires permanent cessation of drug therapy; or
- any immediate respiratory reaction following drug or placebo administration which requires the institution of resuscitative measures which are not immediately (<10 minutes) responsive to interventions and thus requires permanent cessation of drug therapy.

The protocol stipulates that all adverse events occurring during the period of time between the hemodialysis session #2 treatment infusion through completion of study at hemodialysis session #4 are to be documented in the patient's case report form. Events are to be described including clinical course, seriousness and investigator's evaluation of relationship to study drug administration.

For the primary analyses of Ferrlecit versus placebo, using the intent-to-treat population (consisting of all patients who received at least 1 treatment), the sponsor is to compare the two treatments using McNemar's test. For "all allergic events" a comparison using Fisher's exact test also was planned. For primary analyses of Ferrlecit versus iron dextran historical control the sponsor used iron dextran historical control event rates based on a meta-analysis derived from publications. The sponsor's calculated historical event rates for iron dextran were as follows:

Sponsor's Calculated Historical Event Rates for Iron Dextran

Event	Percent (%)	Standard Deviation (%)	95% Confidence Interval
Outcome Adverse Events (OAEs)	2.47	0.31	1.87 , 3.07
Life-Threatening Adverse Events (LTEs)	0.61	0.13	0.36 , 0.86
Total Systemic Reactions[a]	8.41	0.48	7.46 , 9.36

[a] (i.e., "other less severe reactions that are consistent with a highly immunogenic compound, including serum sickness, pain, and rash."

reviewer's table, from information in Study 9803 interim analysis report (NDA Vol. 38.5)

The sample size calculation was based on the comparison of rate of OAEs with Ferrlecit versus rate of OAEs with iron dextran historical control. The sample size for the study (2409 completed patients) assumed an iron dextran OAE rate of 2.47% (based on historical control) and would have 80% power to detect a difference between groups at a 2-sided significance level of 0.05. Secondary calculations determined that the sample size of 2409 completed patients should be able to "detect a difference of 0.56% if the placebo allergy rate is approximately 1%".

Interim Results: Enrollment in Study FER9803 began August 8, 2000. As of April 12, 2000 a total of 1106 patients had been screened at 46 sites and all 1106 of these patients had been enrolled. These 1106 patients are included in the interim analysis report. Enrolled patients had a mean age of 55.1 years (median 56 years, range 19-92 years); 54% are males; 55% are Black, 20%, Hispanic, and 21% Caucasian. Cause of renal failure was documented for only 25% of patients with hypertension (10% of patients) and diabetes (8.3% of patients) being the leading listed causes. About 94% had history of prior exposure to iron dextran; 1-2% of patients had history of anaphylactoid reaction to iron dextran. Twenty-seven percent of patients were on concomitant angiotensin-converting enzyme (ACE) inhibitors.

Seventeen patients withdrew after receiving only one study drug infusion. Seven of these withdrew because of adverse events, 7 withdrew consent and, 3 had significant protocol violations. Adverse events in patients who withdrew after the first infusion were:

Study FER9803 Interim Report: Adverse Events in Patients Discontinuing Study Prematurely

Number of Patients	Event
Ferrlecit:	
1	severe hypotension;
1	possible allergic reaction 2 hrs post study dose, (chills)
1	severe pneumonia*
1	near syncope, exacerbation of hypertension
1	mild pain, back pain, dizziness, insomnia
Placebo:	
1	abdominal pain
1	possible allergic reaction with gastrointestinal symptoms
1	"free iron reaction" (mild nausea, dizziness, headache, vomiting)
1	moderate chills and fever; severe bacteremia, rigor and fever to 103*

1	septic bacteremia*

* These patients are listed as discontinued due to protocol violations.

from sponsor's table

The remaining 1089 patients all received both study drug infusions and completed the study.

Outcome adverse events, life-threatening adverse events, suspected allergic adverse events, and serious adverse events are summarized in the following table:

Study FER9803 Interim Report: Summary of Adverse Events of Interest

Adverse Event	Number of Patients (%)	
	Ferrlecit (N=1097)	Placebo (N=1098)
All Outcome Adverse Events:	8 (0.7%)	2 (0.2%)
allergic reaction	4 (0.4%)	1 (0.1%)
anaphylactoid reaction	1 (0.1%)	0
hypotension	1 (0.1%)	1 (0.1%)
nausea	1 (0.1%)	0
pruritus	1 (0.1%)	0
All Life-Threatening Adverse Events:	1 (0.1%)	0
anaphylactoid reaction	1 (0.1%)	0
Suspected Allergic Adverse Events:	8 (0.7%)	4 (0.4%)
allergic reaction	6[a] (0.5%)	3 (0.3%)
anaphylactoid reaction	1 (0.1%)	0
nausea	1 (0.1%)	0
dizziness	1 (0.1%)	0
pruritus	1 (0.1%)	0
rash	0	1 (0.1%)
Serious Adverse Events:	8 (0.7%)	5 (0.5%)
sepsis	0	3 (0.3%)
anaphylactoid reaction	1 (0.1%)	0
hemorrhage	1 (0.1%)	0
hypertension	1 (0.1%)	0
hypotension	1 (0.1%)	0
nodal tachycardia	1 (0.1%)	0
hypercalcemia	0	1 (0.1%)
pathological fracture	0	1 (0.1%)
subdural hematoma	0	1 (0.1%)
pneumonia	1 (0.1%)	1 (0.1%)
pruritus	1 (0.1%)	0
abortion	1 (0.1%)	0

[a] This includes one patient who was not initially counted in the sponsor's tabulation but was discovered during quality assurance evaluation of the data base

from sponsor's Tables 17.1.1 through 17.1.7

A total of 199 (18.0%) patients reported some adverse event during the study [123 (11.2%) during the Ferrlecit treatment period and 103 (9.4%) during the placebo treatment period]. The most common adverse events were hypotension (2% of patients

for each treatment) and nausea (1.2% of patients with Ferrlecit, 0.8% of patients with placebo). Events reported in 2 or more patients with either treatment are summarized in the following table:

Study FER9803 Interim Report: Most Frequent Adverse Events

Event (preferred term)	Number of Patients (%)	
	Ferrlecit (N=1097)	Placebo (N=1098)
Any Adverse Event	123 (11.2%)	103 (9.4%)
Hypotension	22 (2.0%)	23 (2.1%)
Nausea	13 (1.2%)	9 (0.8%)
Headache	8 (0.7%)	8 (0.7%)
Diarrhea	8 (0.7%)	2 (0.2%)
Hypertension	7 (0.6%)	3 (0.3%)
Allergic reaction	6 (0.5%)	5 (0.5%)
Chest pain	6 (0.5%)	4 (0.4%)
Pain	[illegible]	7 (0.6%)
Pruritus	5 (0.5%)	2 (0.2%)
Asthenia	4 (0.4%)	2 (0.2%)
Abdominal pain	4 (0.4%)	1 (0.1%)
Back pain	4 (0.4%)	1 (0.1%)
Vomiting	4 (0.4%)	4 (0.4%)
Dyspepsia	4 (0.4%)	1 (0.1%)
Malaise	3 (0.3%)	3 (0.3%)
Infection	3 (0.3%)	3 (0.3%)
Vasodilation	3 (0.3%)	1 (0.1%)
Nausea and vomiting	3 (0.3%)	2 (0.2%)
Peripheral edema	3 (0.3%)	0
Dizziness	3 (0.3%)	4 (0.4%)
Hypertonia	3 (0.3%)	2 (0.2%)
Dyspnea	3 (0.3%)	0
Hemorrhage	2 (0.2%)	0
Somnolence	2 (0.2%)	2 (0.2%)
Dry mouth	2 (0.2%)	1 (0.1%)
Nervousness	2 (0.2%)	0
Cough increased	2 (0.2%)	2 (0.2%)
Pharyngitis	2 (0.2%)	1 (0.1%)
Tachycardia	1 (0.1%)	2 (0.2%)
Paresthesia	1 (0.1%)	2 (0.2%)
Sepsis	0	3 (0.3%)
Chills and fever	0	2 (0.2%)
Constipation	0	2 (0.2%)
Parathyroid disorder	0	2 (0.2%)

from sponsor's Table 17.1.8

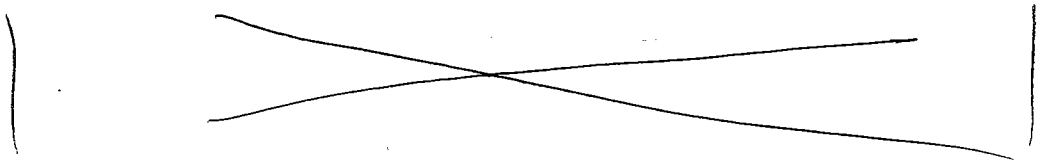
Sponsor's Analyses: The sponsor's analyses of the Ferrlecit data versus iron dextran historical control are summarized in the following table:

Study FER9803 Interim Report: Sponsor's Comparison of Event Rates for Ferrlecit versus Iron Dextran Historical Control

Event	Iron Dextrans	Ferrlecit	p-Value[a]
Drug Intolerance	2.47% (2.16-2.78%) 64/2589	0.73% (0.32-1.43%) 8/1097	<0.001
Life-Threatening	0.61% (0.48-0.73%) 20/3294	0.09% (0.00-0.51%) 1/1097	0.039

[a] based on Fisher's exact test

based on sponsor's tables



The incidences of protocol events for Ferrlecit and placebo in this cross-over study are summarized in the following table:

Table 9 Overall Incidence of Protocol Events (ITT Population)

onfirmed these

Type of Protocol Event[1]	All Treatment Groups N=1106	
	Ferrlecit® N=1098 n (%)	Placebo N=1097 n (%)
Patients with Any Outcome Event[2]	8 (0.73)	2 (0.18)
Patients with Any Life-threatening Adverse Event[3]	1 (0.09)	0 (0.00)
Patients with Any Suspected Allergic Event[4]	8 (0.73)	4 (0.36)
Patients with Confirmed Allergic Event	1 (0.09)	0 (0.00)
Patients with Anaphylactic Event By Protocol	0 (0.00)	0 (0.00)
Patients with a Non-Anaphylactic Allergic Event by Protocol	1 (0.09)	0 (0.00)
Patients with Instantaneous Onset Suspected Allergic Event[5]	3 (0.27)	1 (0.09)
Patients with Immediate-onset Suspected Allergic Event[5]	4 (0.36)	1 (0.09)
Patients with Delayed Onset Suspected Allergic Event[5]	1 (0.09)	2 (0.18)

[1] Not mutually exclusive.
[2] Indicates total number of patients with one outcome event; no patients had more than one.
[3] Indicates total number of patients with one life-threatening adverse event; no patient had more than one.
[4] Indicates total number of patients with one or more suspected allergic adverse event. One patient had two simultaneous suspected allergic events to Ferrlecit® (dizziness & nausea). Includes patients with events that are both outcome events and suspected allergic events (7 patients), and patient with both life-threatening event and suspected allergic event (1).
[5] Instantaneous was defined as an event that began during study drug infusion. Immediate-onset was defined as an adverse event that occurred after infusion but before dialysis was completed. However, one patient is identified in the database as an "immediate" reaction who did not report the reaction until the next hemodialysis session. [redacted] 078 indicated retrospectively that the event of GI cramping began in the last ten minutes of the post-study drug HD session. On this table, this reaction is identified as a delayed reaction since it outside the 2 hour window for mast cell activation reactions.
Data Source: End-of-Text Tables [illegible], 17.1.2, 17.1.3, and 17.1.12; Listing 10.1

The sponsor compared incidence of suspected allergic events and incidence of confirmed immediate allergic events for Ferrlecit versus placebo in this interim analysis. These analyses are summarized in the following table:

Study FER9803 Interim Report: Sponosr's Comparison of Event Rates for Ferrlecit versus Placebo

Event	Ferrlecit	Placebo	p-Value[a]
Suspected Allergic Events	0.73% (0.32-1.43) 8/1097	0.36% (0.10-0.93) 4/1098	0.265
Confirmed Immediate Allergic Events	0.09% (0.00-0.51%) 1/1097	0% (0.00-0.33%) 0/1098	0.500

[a] based on Fisher's exact test

sponsor's table

Confidence intervals for these event rates in the two arms overlapped.

Discussion and Comments Regarding the Proposed Labeling Changes:

The iron dextran historical control is based on three publications (Hamstra, Fishbane and Faich) and product labeling for Feridex. [One additional publication was excluded because total number of patients treated was not known]. Adverse event rates for iron dextran in these publications are summarized in the following table:

Meta-analysis: Adverse Event Rates for Individual Publications

	Feridex	Hamstra	Fishbane	Woodman	Faich
	N=2240	N=481	N=573		N=474
Rate of life-threatening allergic or anaphylactic reactions	0.5%	0.62%	0.7%	1.8%	1%
Severe reactions (requiring permanent drug withdrawal)	2.15%	1.87%	3.84%		no data

By performing a meta-analysis of the Feridex, Hamstra, Fishbane and Faich data, the sponsor calculated the following overall event rates for the iron dextran historical control.

Meta-analysis: Overall Event Rates

Event	Percent (%)	Standard Deviation (%)	95% Confidence Interval
Outcome Adverse Events (OAEs)	2.47	0.31	1.87 - 3.07
Life-Threatening Adverse Events (LTEs)	0.61	0.13	0.36 – 0.86
Total Systemic Reactions[a]	8.41	0.48	7.46 – 9.36

[a] i.e., "other less severe reactions that are consistent with a highly immunogenic compound, including serum sickness, pain, and rash."

Important differences among the studies are summarized in the following table:

Differences between the published iron dextran studies and FER9803

Differences	Hamstra (N=481)	Fishbane (N=573)	Feridex (N=2240)	Faich (N=474)	FER9803 (N=1106)
Design	Prospective	Retrospective	Prospective	Retrospective	Prospective
Study period	1962-1970	1993-1995	1988-1992	1996	1999
Population	General iron deficiency anemia patients	Hemodialysis patients	Suspected liver disease undergoing MRI	Hemodialysis patients	Hemodialysis patients
Iron dextran formulation/ Ferrlecit	Imferon: withdrawn in 1991	INFed	Feridex: contrast agent for MRI of liver	Unspecified iron dextran	Ferrlecit
Outcome assessment: Life-threatening event Drug Intolerance event	Life-threatening immediate anaphylactoid reactions Discontinued due to severe reactions	Severe reactions Discontinued due to adverse events	Anaphylactic and allergic adverse events Discontinued infusion because of acute, moderate to severe pain	Use of iron dextran and epinephrine during the same hospital stay Unavailable	Any immediate hypotensive/ respiratory reaction which were not immediately (<10 minutes) responsive to the interventions. Any event that was sufficient to preclude re-exposure to the drug substance.
Number of dose exposure	4-5 doses	10 doses	1 dose	unspecified	1 dose

Reviewer's table

table from Medical Officer's Review

Most of the patients in the meta-analysis were from a study of Feridex, an iron dextran contrast agent. Two studies involved patients receiving multiple doses of iron dextran. The reports from these studies do not identify whether patients experienced the noted adverse event on the first or a subsequent exposure. In FER9803 patients received a single dose of Ferrlecit. In the Fishbane study a strong association between reaction to iron dextran and history of drug allergy (not including iron dextran), especially multiple drug allergy, was noted. Proportion of patients with history of drug allergy in this study is not given. Two of the studies were retrospective. No clinical protocols, raw data or other supporting materials are provided for any of the studies used in the iron dextran meta-analysis.

The sponsor has provided estimates of U.S. utilization and a report of spontaneous adverse events reported for iron dextran (INFeD and Dexferrum) and Ferrlecit (NDA Vol 38.10, Tabs VI.C.3 and VI.C.4). In 1999 about [redacted] of INFeD, about [redacted] of Dexferrum and about [redacted] of Ferrlecit were utilized. From January through mid-April 2000 about [redacted] of INFeD, about [redacted] Dexferrum and about [redacted] Ferrlecit were utilized. [Note: INFeD and Dexferrum were the only two iron dextran products marketed in the U.S during this time]. Based on these figures market share of Ferrlecit increased from about 4.1% in 1999 (launch to end of year) to about 12.7% in January-April 2000. Thus, it appears that an increasing proportion of patients requiring intravenous iron are receiving Ferrlecit.

Serious adverse events for iron dextran products for 1998 and 1999 are summarized in the sponsor's table below. For this report serious adverse events were defined as: death, life-threatening, leading to hospitalization (initial or prolonged), disability, congenital abnormality or required intervention to prevent permanent damage.

Overall Summary Tables

Serious Reports				
Drug	Expedited Reports	Periodic Reports	Direct Reports	Total Reports
Dexferrum	7	18	33	58
Infed	21	18	12	51
Iron Dextran NOS	4	0	11	15
Non-Serious Reports				
Drug	Expedited Reports	Periodic Reports	Direct Reports	Total Reports
Dexferrum	0	11	22	33
Infed	0	41	5	46
Iron Dextran NOS	0	6	2	8
All Reports				
Drug	Expedited Reports	Periodic Reports	Direct Reports	Total Reports
Dexferrum	7	29	55	91
Infed	21	59	17	97
Iron Dextran NOS	4	6	13	23

Iron dextran associated deaths for 1998 were reported as follows:

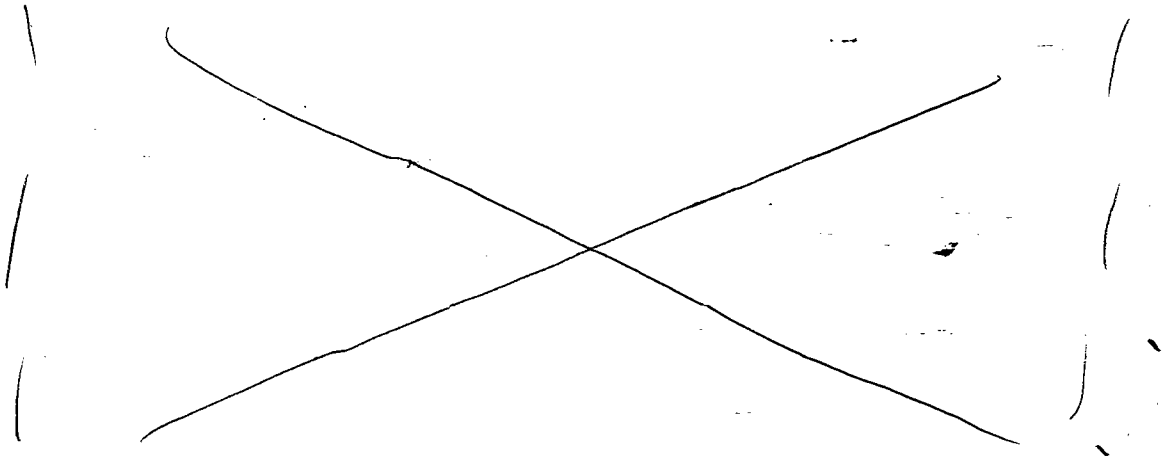
Sponsor's Summary of Iron Dextran Associated Deaths

	Number of Patients	
Year	1998	1999
INFeD	6	5
Dexferrum	8	6
iron dextran NOS*	1	0
Total	15	11

*not specified

based on sponsor's report

FDA Office of Post-Marketing Risk Assessment (OPDRA) review of serious adverse events associated with iron dextran products from February 1, 1998 to January 31, 2000 found 17 reports of death for Dexferrum [ANDA 40-024] of 293 ADEs reported (5.8%) . During the same time, 9 deaths were reported for INFeD [NDA 17-441] out of 171 reports ADEs (5.3%)(OPDRA Medical Officer Review dated March 1, 2000).



In addition to the Study FER9803 interim analysis the sponsor has provided preliminary results from 919 patients enrolled in Study FER9803 since closing off the database for the interim analysis, results from 283 patients in literature publications and results from 159 patients who have participated in other North American studies of Ferrlecit. The sponsor states that only one protocol event has occurred in the 919 additional FER9803 patients – one patient [treatment still blinded] with principal clinical symptom of low back pain which was classified as an outcome (drug intolerance) and suspected allergic event (increase in tryptase values). No data listings or other information regarding these 919 patients is included in the current submission. Among the remaining 442 patients the sponsor states that "not a single patient has yet had a serious adverse reaction accompanied by tryptase elevation."

The total body of safety information available for Ferrlecit is reassuring in that there does not appear to be an unusually high rate of serious allergic events with Ferrlecit, though anaphylactoid reactions do occur at a low rate. As of January 8, 2001the FDA AERS database contains reports of death in patients on Ferrlecit; (Ferrlecit was listed as suspect drug for only 2 of these). None of these appear to have been due to allergic events. The AERS database contains 98 reports of serious adverse events with Ferrlecit. There are 13 reports of "allergic" reaction, one report of "anaphylactoid" reaction and no reports of "anaphylactic" reaction. There are reports of 26 cases of hypotension associated with Ferrlecit. There are no reported cases of flushing associated with Ferrlecit in the AERS database. Considering the available information it is reasonable at this time to modify the description of hypersensitivity reactions in the Ferrlecit labeling. It would be reasonable to move the hypersensitivity discussion to the beginning of the PRECAUTIONS section of the labeling. Probably an abbreviated WARNINGS section should be retained stating the following: "Warnings: Hypersensitivity reactions have been reported with injectable iron products. (See PRECAUTIONS)." The sponsor should continue to monitor the safety database for Ferrlecit for occurrences of allergic reactions and provide a summary report of these events to the Agency quarterly.Hypotension and flushing should be listed in the adverse events section as these do occur in the Ferrlecit database. The spontaneous reporting system database should continue to be monitored for serious allergic events.

Administration of Ferrlecit to patients in FER9803 generally was well-tolerated and it is therefore reasonable to remove the requirement for a test dose from the Ferrlecit DOSAGE AND ADMINISTRATION instructions. Similarly, administration of Ferrlecit by slow injection — over 10 minutes) was well-tolerated in Study FER9803 and may be included in the dosing recommendations in the labeling.

The sponsor also proposes changes to the DESCRIPTION and CLINICAL PHARMACOLOGY sections of the labeling. The proposed changes add some information about characteristics and stability of the drug (in the DESCRIPTION section) and results of single dose intravenous pharmacokinetic studies and modeling of those results and other PK/PD information (in the CLINICAL PHARMACOLOGY section). The information added to the CLINICAL PHARMACOLOGY section

The changes in the DESCRIPTION and CLINICAL PHARMACOLOGY sections are being reviewed by FDA Chemistry and FDA Biopharmaceutics, respectively.

Conclusions and Recommendations:
The sponsor has in accordance with the Phase 4 agreement conducted a study to gather additional information on the safety of Ferrlecit. Study FER9803 should continue to completion. Recommendations for the Ferrlecit labeling include:

- Descriptive information about Study FER9803 should be included in the labeling.
-
- The information about allergic reactions and hypotension moved from the WARNINGS section of the label to the PRECAUTIONS section. Probably an abbreviated WARNINGS section should be retained stating the following: "Warnings: Hypersensitivity reactions have been reported with injectable iron products. (See PRECAUTIONS)." The sponsor should continue to monitor the safety database for Ferrlecit for occurrences of allergic reactions and provide a summary report of these events to the Agency quarterly.
-
-
- Any adverse events occurring with Ferrlecit exposure in the Study FER9803 that are not currently mentioned in the ADVERSE EVENTS section of the labeling should be added under the appropriate category.
- The requirement for a test dose of Ferrlecit may be removed from the DOSAGE AND ADMINISTRATION instructions.
- Administration of Ferrlecit by slow injection (125 mg over 10 minutes) may be included in the dosing recommendations in the labeling.
-

Final results of Study FER9803 should be submitted when available and the remaining Phase 4 commitments for Ferrlecit should be completed.

cc:
NDA 20-955
HFD-180/Division File
HFD-180/BStrongin
HFD-180/KRobie-Suh
HFD-180/MLu
HFD-720/TPermutt
HFD-180/JChoudary
HFD-180/LZhou

APPENDIX A

(Sodium ferric gluconate complex in sucrose injection)

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® 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 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 Ferrlecit® 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 40.

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 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 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 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 62.5 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.

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 9.1 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 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

Study B	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 anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin 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 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 62.5 MG OF ELEMENTAL IRON WERE ADMINISTERED OVER 30 MINUTES, AND DOSES OF 125 MG 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/m²/day) in mice and 20 mg/kg/day (120 mg/m²/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/m²/day) for a person of 50 kg body weight, average height and body surface area of 1.46 m². 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 or 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

Exposure to Ferrlecit® has been documented in 385 patients on hemodialysis. 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 any hypotension in patients who received Ferrlecit® 62.5 mg of elemental iron over 30 minutes was similar to the incidence of hypotension in patients who received Ferrlecit® 125 mg 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 (3.4%) 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 1000 mg 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(i)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 300 µg/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 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.

DOSAGE AND ADMINISTRATION

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

Before initiating therapeutic doses of Ferrlecit®, administration of an intravenous test dose of 2 mL Ferrlecit® (25 mg of elemental iron) is recommended. This test dose should be diluted in 50 mL 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 10 mL of Ferrlecit® (125 mg 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°C-30°C (59°F-86°F). See USP Controlled Room Temperature.

Caution: Rx Only

SCHEIN

R&D

/s/

Kathy Robie-Suh
1/31/01 05:34:30 PM
MEDICAL OFFICER

Lilia Talarico
2/1/01 05:59:52 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-955/S-003

CHEMISTRY REVIEW(S)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls Supplement

NDA#:20-955SUPPLEMENT#:SE8-003 CHEM REVIEW#:1REVIEW DATE:11/21/00

SUBMISSION TYPE	DOCUMENT ST	CDER	DATES ASSIGNED	REVIEW	NUM	LETTER
ORIGINAL	8/2/00	8/2/00	8/8/00	11/21/00		

SUPPLEMENT PROVIDES FOR:
Changes to labeling.

NAME & ADDRESS OF APPLICANT: R & D Laboratories, Inc.
4640 Admiralty Way, Suite 710
Marina del Rey, CA 90292

DRUG PRODUCT NAME:

Proprietary:	Ferrlecit® Injection
Nonproprietary/USAN:	Ferric Sodium Gluconate Complex in Sucrose Injection
Code Name/#:	8012004
Chem.Type/Ther.Class:	1/P

PHARMACOLOGICAL CATEGORY: Hematinic

INDICATION: Treatment of acute and chronic iron deficiency in renal hemodialasis patients receiving supplemental erythropoietin therapy.

DOSAGE FORM: Injection

STRENGTH: 62.5 mg elemental iron/5 mL

ROUTE OF ADMINISTRATION:

HOW DISPENSED: X Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
Sodium ferric gluconate complex in sucrose solution

$[NaFe_2O_3(C_6H_{11}O_7)(C_{12}H_{22}O_{11})_5]_{200}$ (proposed)

Mol. Wt. = 350,000 ± 23,000 daltons (proposed)

9 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-20955
5033

SUPPORTING DOCUMENTS:

DMF Number	Item referenced	Holder	Status	Review Date	Letter Date
None					

RELATED DOCUMENTS (if applicable): N/A

CONSULTS: None.

REMARKS/COMMENTS:
Reviewed proposed labeling changes affecting CMC information (in DESCRIPTION, CLINICAL PHARMACOLOGY (pharmacokinetics), OVERDOSAGE, HOW SUPPLIED.

CONCLUSIONS & RECOMMENDATIONS:
Not approvable.

Raymond P. Frankewich, Ph.D.
Review Chemist, HFD-180

Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-180

cc:
NDA #20-955
HFD-180/LTalarico
HFD-180/Div File/NDA #20-955
HFD-180/LZhou
HFD-180/RFrankewich
HFD-181/BStrongin
R/D Init by: LZhou/11-15-00
RF/rpf Draft 11-15-00/F/T 11-21-00
W:c: /wordfiles/chem/N/20955003.1rf

/s/

Ray Frankewich
11/22/00 11:01:50 AM
CHEMIST

Review completed 11/21/00. Author signed 11/22/00.

Liang Zhou
11/22/00 01:04:26 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-955/S-003

STATISTICAL REVIEW(S)

STATISTICAL NDA REVIEW AND EVALUATION

Date: **January 8, 2001**

NDA: 20-955/SE8-003

APPLICANT: R&D Laboratories.

NAME OF DRUG: Ferrlecit (sodium ferric gluconate complex in sucrose) Injection.

APPROVED INDICATION: Treatment for iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental recombinant erythropoietin therapy.

USER FEE DUE DATE: Feburary, 2, 2001.

DRUG CLASSIFICATION: 1P.

DOCUMENT REVIEWED: NDA Volumes 38.1 to 38.10, dated August 2, 2000; NDA Document dated October 5, 2000.

MEDICAL REVIEWER: This review has been discussed with medical officer, Min Lu, MD.

STATISTICAL REVIEWER: Wen-Jen Chen, Ph.D.

1.0 . INTRODUCTION

In the submitted Volume 38.5, the sponsor made the following reservations with regard to Ferrlecit:

> Anemia in the patient with End Stage Renal Disease (ESRD) is primarily related to a deficiency in the endogenous production of epoetin. After epoetin deficiency has been corrected, however, the anemia is complicated by the chronic continuing blood loss induced iatrogenically by dialysis. Ferrlecit is a product for the administration of iron intravenously in patients with iron deficiency anemia in whom oral use is unsatisfactory or impossible. In controlled clinical studies with Ferrlecit, oral iron supplementation has been shown to be ineffective in keeping up with iron losses in hemodialysis patients on epoetin. This loss has attributed to chronic blood loss in dialysis tubing, diagnostic venipunctures, and an increase in normal gastrointestinal tract losses from coagulopathy. Hemodialysis (HD) patients, therefore, generally require both epoetin and intravenous iron replacement therapy to manage the anemia.

As it was stated in the proposed package insert amendment section of Volime 38.1, the purpose of this NDA supplement is mainly to request the following labeling changes for the above approved indication:

sponsor submitted the results of comparing event rates from three historical control studies (Hamstra, Fishbane, and Feridex) for iron dextran with those of Ferrlecit performed in the concurrent study FER 9803.

the sponsor submitted the results of comparing event rates from Ferrlecit with those of placebo using a cross over design performed in the concurrent study FER 9803.

2.0 STUDY# FER 9803

2.1 Background Information

Objectives: The primary objectives of this study were as follows:

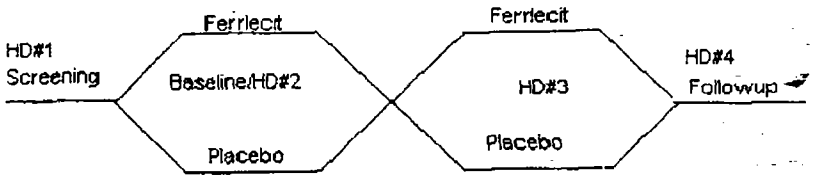
- To compare drug intolerance (outcome events) and life-threatening adverse events (LAEs) after Ferrlecit administration to the same defined events following iron dextran administration derived from the meta-analysis.
- To compare the incidence of all immediate-type allergic reactions following Ferrlecit administration to those following placebo administration both with and without verification of allergenicity using the rise in serum tryptase level.

Study Design: This was a multi-center, crossover, randomized, double-blinded, prospective, comparative study for the safety of sodium ferric gluconate complex in Ferrlecit sucrose injection in iron deficient, anemic, hemodialysis patients versus two controls—placebo and iron dextran. This multi-center study was conducted at up to 100 sites. A total of 2,700 patients was enrolled across these sites to ensure that at least 2,409 patients receive both Ferrlecit® and placebo infusions.

Patients who signed the informed consent and satisfy the selection criteria might enter the study and participate over the course of four sequential dialysis sessions. At the first hemodialysis session (HD#1 session), patients who provide informed consent will undergo screening procedures consisting of medical history (including demographics, duration on hemodialysis, cause of renal failure, review of current medications, asthma and allergy, prior parenteral iron exposure, assessment of response to dialysis), physical examination, and clinical laboratory assessments. Patients would be evaluated based on inclusion and exclusion criteria.

At HD#2 section, patients deemed eligible and who provided informed consent for participation in the study would be randomized to one of two crossover treatment schedules: Ferrlecit at HD#2 and placebo at HD#3 or placebo at HD#2 and Ferrlecit at HD#3. Finally, HD#4 was the adverse event follow-up visit. A schematic of the study is presented in Figure 1.

Figure 1 Study Design Schematic



It is noted that for Ferrlecit, the cross over design was conducted to collect the life threatening and drug intolerance events while for iron dextran, those events were from historical controls: Hamstra, Fishbane, and Feridex. [In protocol stage, those two adverse event rates for iron dextran were planed to acquire from the four historical controls: Hamstra, Fishbane, Feridex, and Faich.]

Drug Administration: A total of 125 mg of Ferrlecit (10 mL) would be administered undiluted by slow intravenous injection over a period of ten minutes. Placebo would be composed of 10 mL of saline containing 9 mg/mL of benzyl alcohol and would be administered over the same time period.

Unblinded personnel would prepare placebo or Ferrlecit, which would be covered with appropriate materials to maintain blinding of the treatment. This would ensure that study personnel administering treatment and completing the case report forms, and the patient remained blinded. Drug would be administered during the first 60 minutes of hemodialysis.

Monitoring: Vital signs would be recorded before, during, and after administration of study drug. Patient signs and symptoms would be recorded on the case report form (CRF) before and after infusion. Blood pressure and pulse would be recorded at baseline, at 5 minutes into the injection, and at 5 and 20 minutes after completion of the infusion. In the event that a patient experiences symptoms and/or a hypotensive episode during dialysis, additional measurements would be obtained as appropriate. The duration of the dialysis session would also be recorded on the CRF.

Observations at 5 and 15 minutes after initiation of the injection at HD#2 and HD#3 for signs and symptoms of a possible allergic reaction would be recorded. Administration of study drug would begin and end in the first hour after initiation of dialysis.

At the beginning of HD#3 and HID#4, patients would be assessed for any adverse reactions since the preceding HD session at which drug substance had been given. Upon completion of this assessment at HD#4, the study was completed.

Study Population: The inclusion criteria for the study population included the following patients: adult male or female hemodialysis patient providing written informed consent; on supplemental erythropoietin therapy for >120 days; etc. The exclusion criteria excluded the following patients: prior treatment with Ferrlecit; known sensitivity to benzyl alcohol; first use of a dialyzer membrane; and acute or chronic therapy with antihistamines or corticosteroids; etc.

(For detail of the study population, refer to the section 8.3 Selection of Study Population in Volume 38.5 submitted by the sponsor)

Drug Dispensing: In order to maintain double-blind status, the Principal Investigator designated a representative outside of the study personnel who was responsible for dispensing the clinical supplies, covering and blinding the clinical supplies for administration by blinded personnel, exercising accepted medical and pharmacy practices, and maintaining accurate records of dispensing all study drug.

Patient Numbering: Each patient would be assigned a temporary screening number at the first visit (I-ID #1). A randomization number would be assigned to each qualified patient at HD#2. This randomization number would consist of a two-digit site identification number followed by a three-digit patient number.

Randomization: Each center would be provided with study kits containing placebo, labels, 10 mL syringes, Ferrlecit ampules, and appropriate materials for blinding. Randomization sequences would be computer generated. Randomization would occur at HD#2. Patients who met all eligibility criteria would be randomly allocated following all baseline evaluations using a 1:1 ratio to 2 groups: initial treatment with ferric sodium gluconate in sucrose injection (Ferrlecit) or with placebo. Each patient would then crossover to the alternate treatment during the next hemodialysis session.

Outcome Assessment: The following outcome assessments were conducted: drug intolerance events, life-threatening events, blood pressure, pulse, allergic adverse events, and Tryptase as an indicator of immunologically mediated reactions.

Disposition of Patients: For the interim analysis stage, 1106 iron-deficient, anemic, hemodialysis patients were enrolled at 46 study centers and received at least one infusion (ITT population). Of these patients, 1089 received both Ferrlecit® and placebo and were included in the per-protocol population. Table 2.1.1 summarizes the patient disposition.

Table 2.1.1(Sponsor's) Summary of Patient Disposition

Disposition	All Treatment Groups (N=1106)	
Number of Patients Enrolled	1106	
Intent-to-Treat Patients[a]	1106	
Number of Patients Discontinued after HD#2	17	
Number of Patients Discontinued by Treatment	8 (Feerlecit only)	9 (placebo only)
Per-Protocol Population[b]	1089	
Per-Protocol Population by Treatment	1097 (Ferrlecit)	1098 (placebo)
Number of Patients Completed the Study	1089	

[a]: patients who completed at least HD#2.

[b]: Patient population for secondary analysis; patients who completed HD#2 and 3. Analyses for the per-protocol population was not performed for this interim report. HD = Heniodialysis.

[One notes that the sponsor's interim analyses on the three primary adverse events, life threatening, drug intolerance, and all allergic events, reported by this submission, were using the Per-Protocol population by treatment.]

Primary Adverse Event: Three primary adverse events considered in this study were drug intolerance events – Ferrlecit versus iron dextran, life-threatening adverse events – Ferrlecit versus iron dextran, and all (drug) allergic events – Ferrlecit versus placebo.

Primary Analysis: For drug intolerance and life threatening events, the primary analysis was to compare the two-sided 68% confidence interval (historical adverse event rate ± standard deviation) on the adverse event rate for the iron dextran historical control group to the two-sided exact 95% confidence interval for the Ferrlecit treatment group.

The algorithm proposed by the sponsor for the comparisons of the above two primary adverse event rates between Ferrlecit and iron dextran were stated below:

- If the upper bound of the two sided exact 95% confidence interval for Ferrlecit was found to fall below the Historical adverse event rate – standard deviation for iron dextran then it would be concluded that this study arm was positive.
- If the Exact 95% confidence interval for Ferrlecit covers the Historical adverse event rate ± standard deviation for iron dextran then it would be concluded that the study arm was identified as indeterminate.
- If the lower bound of the Exact 95% confidence interval for Ferrlecit was found to fall above the Historical adverse event rate + standard deviation for iron dextran then it would be concluded that this study arm was negative.

However, as for the drug allergic events, the difference of the event rates between placebo and Ferrlecit was compared by McNemar test. If the rate of all (drug) allergic reactions to Ferrlecit was either significantly less than or significantly indistinguishable from placebo, the comparison would be considered positive; otherwise would be considered as negative.

Finally, the sponsor concluded that with respect to the three foregoing outcome analyses, the study results were considered positive if all of the aforementioned comparisons were positive and none of the other comparisons were negative. The study results would be considered negative if any of the aforementioned comparisons was negative.

The primary adverse event rates were analyzed for the following two groups of patients:

- Intent-to-treat population- patients who entered the study and received at least one treatment,
- Per protocol population- patients who received study infusions with both Ferrlecit and placebo.

The applicant purported that the primary adverse event analysis was the analysis from the Intent-to-treat (ITT) patients.

2.2 Sponsor's statistical analysis and results

Analysis of demographics and baseline characteristics

It should be noted that the results of the demographics and baseline characteristics analysis were presented only for those patients enrolled into this clinical study. The sponsor indicated that of the 1106 patients enrolled into this study, 54.4% (602/1106) were male, 55.3% (612/1106) were Black, 21.4% (237/1106) were Caucasian, 20.0% (221/1106) were Hispanic, and the median age was 56 years. The ranges in height, weight, and blood pressure (both systolic and diastolic) were broad. The majority of the patients (93.5%; 1034/1106) had prior parenteral iron dextran exposure: 79.9% (884/1106) were exposed to InFeD, 9.8% (108/1106) were exposed to Oexferrum, and 3.8% (42/1106) were exposed to both. Of these 1034 patients who had prior parenteral iron exposure, 72 (7.0%) patients had prior sensitivity to at least one form of iron dextran. This represents 6.5% (72/1106) of total enrollment for this interim report.

Analysis of sponsor's Efficacy Analysis Results

Primary analysis results

Table 2.2.1 presents the sponsor's analysis results for the following three primary adverse events using Per-Protocol (PP) population by treatment: drug intolerance, life threatening, and all (drug) allergic adverse events.

Table 2.2.1 (Sponsor's) The analysis results for the primary adverse events using PP population

EVENT	IRON DEXTRAN	FERRLECIT	PLACEBO	PROTOCOL VALUE
Drug-Intolerance	2.47%[a] 2.16% - 2.78%[b] 64/2589	0.73% 0.32% - 1.43% 8/1097	NA	**Positive**
Life-Threatening	0.61% 0.48% - 0.73% 20/3294	0.09% 0.00% - 0.51% 1/1097	NA	**Indeterminate**
Suspected Allergic Events	NA[c]	0.73% 0.32% - 1.43% 8/1097	0.36% 0.10% - 0.93% 4/1098	**Positive (p=0.265)[1]**
Confirmed Immediate Allergic Events	NA	0.09% 0.00% - 0.51% 1/1097	0% 0.00% - 0.34% 0/1098	**Positive (p=0.50)[1]**

[a]: Adverse event rate; [b]: Two-sided confidence interval – 68% for Iron dextran and 95% for Ferrlecit; [c]: Not applicable for protocol events. [1]: Ferrlecit versus placebo by Fisher's exact test using parallel design.

Based on the interim analysis results presented by Table 2.2.1, the sponsor made the following conclusions:

- With regard to the predefined primary analyses, for drug intolerance, Ferrlecit was identified as positive when comparing with Iron-dextran since the upper bound (1.43%) of the Exact 95% confidence interval for Ferrlecit was smaller than the lower bound (2.16%) of iron dextran.
- With regard to the predefined primary analyses, for life threatening, Ferrlecit was identified as indeterminate when comparing with Iron-dextran, since there was an overlap between two confidence intervals.
- With regard to the predefined primary analysis, for all (drug) allergic events, Ferrlecit is identified as positive when comparing with placebo, since the all allergic events for Ferrlecit were not statistically significantly different from those of placebo when assessed by suspected

allergic events (p=0.265) and confirmed allergic reactions (p=0.50).

Since the results for life-threatening is identified as indeterminate, based on the sponsor's pre-defined criteria on the three foregoing outcome analyses, even without interim look adjustment, this study results on the three primary adverse events can not be considered positive.

2.3 Reviewer's Comments

One notes that the two primary adverse events (life threatening and drug intolerance) from three historical control studies (Hamstra, Fishbane, and Feridex) for iron dextran were used by the sponsor in the safety comparisons between Ferrlecit and Iron-dextran. In addition, the rates of all allergic event occurrences were compared for Ferrlecit versus placebo through a cross over design analysis. This reviewer therefore, comments on the following issues with regard to the use of the historical controls, the identification of all allergic event, and the statistical methods applied by the sponsor to the primary adverse events (life threatening, drug intolerance, and all allergic):

I. The issue on the use of historical trials for the active control drug.
II. The issue on the adequacy of the three selected historical trials.
III. The issue on the identification of all allergic event.
IV. The issue on the primary adverse event analysis.

Since the above first two issues are related to the historical control studies, this reviewer applies the criteria proposed by Pocock in his paper entitled " The combination of randomized and historical controls in clinical trials" published by J Chron Dis. 1976, Vol. 29, pp. 175-188 to comment the issues on the use of historical trials and the inadequacy of the selected historical controls. As for the adequacy of a historical control used with a randomized concurrent study in clinical trials, Pocock emphasized in his paper that the acceptability of a historical control group requires that it meets the following six conditions:

1) Such a group must have received a precisely defined standard treatment which must be the same as the treatment for the randomized controls.
2) The group must have been part of a recent clinical study, which contained the same requirements for patient eligibility.
3) The methods of treatment evaluation must be the same.
4) The distributions of important patient characteristics in the group should be comparable with those in the new trial.
5) The previous study must have been performed in the same organization with largely the same clinical investigators.
6) There must no other indications leading one to expect differing results between the randomized and historical controls.

<u>Comment on issue I – The improper use of the historical active control trials</u>

As stated in the introduction section,

This reviewer therefore, would like to comment on the legitimacy for the use of the historical trials by the light of regulatory rules. By the section of labeling for human prescription drugs (§ 201.57) in code of federal regulations, it clearly states that any claim comparing the drug to which the labeling applies with other drug in terms of frequency, severity, or character of adverse reactions shall be based on adequate and well-controlled studies as defined in section § 314.126(b). In the section of adequate and well-controlled studies (§ 314.126(b)), it comments that because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent populations, historical control designs are usually reserved for special circumstances, for example studies of diseases with high and predictable mortality (ethic issue). The similar comments on the historical controls are found in the paper of Pocock (1976). Pocock commented that the major problem with historical controls is that one is unable to ensure comparability between the groups of patients and methods of evaluation for the new and standard treatment.

As indicated in the introduction of the sponsor's protocol, like Ferrlecit, iron dextran is also an intravenous iron formulation for hemodialysis patients to manage the anemia. Thus, there was no ethical reason for not including iron dextran in Study FER9803 as an active treatment concurrent control.

Comment on issue II – The inadequate selections on the three historical trials

As the reason stated in the section of the comment on Issue I, this reviewer comments on the issue for the in-adequate selections with regard to the three historical controls: Hamstra, Fishbane, and Feridex. Since no individual patient data set on the three selected historical control trials (Hamstra, Fishbane, and Feridex) were provided by the sponsor, based on the publications for the above three historical control studies, this reviewer comments on the issues listed below.

i.) The heterogeneity across the eligible patient populations.

In order to ensure differences on the primary adverse event rates truly due to treatments Ferrlecit and Iron dextran, it is extremely important that the study patient populations enrolled for the two treatment groups should follow the same requirements for patient eligibility and are comparable on both demographics and baseline clinical characters. However, patients selected by the two historical control studies Hamstra and Feridex were different from those in study Ferrlecit. For Hamstra historical study, the study patients were iron deficient, rather than hemodialysis patients. In addition, the Hamstra study had more females than those did in Ferrlecit study. As to the historical study Feridex, the objective was for liver enhancement during MRI rather than for

treatment of anemia. Therefore, patients enrolled into Feridex study mainly were known or suspected to have liver lesions rather than hemodialysis patients.

Currently, one is lack of medical knowledge to ensure that there is no significant impact of the effect for the patient population heterogeneity on the comparisons of drug intolerance and life threatening adverse events between Ferrlecit and historical controls. In addition, the population heterogeneity between historical controls and concurrent trial violates the second and the fourth requirements, proposed by Pocock, for the acceptability of a historical control group. Therefore, the issue on the population heterogeneity should be considered critical.

ii.) The bias on the assessment of adverse events.

It is noted that the recognition on the symptoms for the two primary adverse events, drug intolerance and life threatening, is unable to be clearly identified (like death). Therefore, the bias on the assessments for the above two primary adverse events is induced due to the following factors and results in an in-appropriate comparisons on the adverse events between Ferrlecit and the three selected historical studies (Hamstra, Fishbane, and Feridex):

- Since the three selected historical control studies and the concurrent trial Ferrlecit were conducted in different time periods, it is very likely that among theses four studies, different assessment standards were applied to identify the events of drug intolerance and life threatening, resulting in an inconsistent assessments. Clearly, the third requirement for a valid historical control study, proposed by the Pocock, is violated by the selected historical controls.
- Different investigators from different centers assessed the adverse events on the three selected historical studies and the concurrent Ferrlecit trial. Therefore, the variation on the recognition of adverse event was induced by the investigators and no adjustment on the center effect when comparing the adverse events between Ferrlecit and iron-dextran can be performed. The adverse events assessed by the different investigators violate the fifth requirement of an acceptable historical control trial proposed by Pocock.

Strictly speaking, inconsistency in the evaluation on the two primary adverse events, drug intolerance and life threatening, and the variation between investigators can seriously interfere with any historical comparisons (Pocock, 1976).

iii.) Adverse events assessed from repeat doses

The issues with regard to drug intolerance and life threatening assessed from repeat doses for selected historical controls are given below:

- The drug intolerance events for historical control study Hamstra were based on total of 2099 drug injections in 481 patients rather than based on single first dose as it did in the concurrent Ferrlecit trial.
- The severe reactions (defined as life threatening events considered by the sponsor) and drug

intolerance events collected from the historical control study Fishbane were from repeat exposure rather than from single first dose as it did in the concurrent Ferrlecit trial.

One notes that the two primary adverse events, drug intolerance and life threatening, were identified from repeat doses for historical trials, Hamstra and Fishbane, and from single first dose for concurrent trial Ferrlecit. Therefore, the comparison of adverse events between the historical controls, Hamstra, Fishbane, and Feridex, and the concurrent trial Ferrlecit is not appropriate. The results for the adverse event comparisons are biased toward in favor of Ferrlecit. Clearly, patients in historical controls administered by repeated doses violate the first requirement, proposed by Pocock, for an acceptable historical control.

iv.) Adverse events assessed from in-correct dose

As noted from the publications, the doses used for the following historical controls were not equal to the current recommended iron dextran dose (100 mg):

- The study drug dosage administrated in the historical control study Hamstra was much higher than the recommended iron dextran dose (100 mg) used in hemodialysis patients.
- The molecular weight and combination of iron dextran for the historical control study Feridex were different from the current iron dextran preparation for the treatment of anemia patients. In addition, the drug dosage used in Feridex was also different from the recommended iron dextran dosage.

Due to different compound structure and different doses, the two historical control studies, Hamstra and Feridex, selected for the comparisons of drug intolerance and life threatening between Ferrlecit and iron dextran are inappropriate. Again, this case violates the first requirement proposed by Pocock for an acceptable historical control.

Overall comments/conclusions on the three selected historical controls

As commented in the above four critical issues with regard to the inadequate selections on the three historical controls, one notes that five of the six acceptability requirements for a historical control group proposed by Pocock are violated. In addition, there are at least two other indications stated below leading one to anticipate incorrect results on the comparisons of life-threatening and drug intolerance between Ferrlecit and the three selected historical trials: 1.) patients from the historical controls were not randomly selected from the same population as the Ferrlecit group; 2.) since the historical controls were conducted in earlier time (for example Hamstra in 1962), patients entering the new trial may receive superior medical care and supervision which contributes to the 'placebo effect' that mere entry into a clinical trial improves the patient's ability to respond. These two indications violate the sixth requirement for an acceptable historical control proposed by Pocock.

In Pocock's paper, he clearly emphasized that only if all these six conditions are met can one

safely use the historical controls as part of a randomized trial. Otherwise, the risk of a substantial bias occurring in treatment comparisons cannot be ignored. Following the comment on issue II and the above overall comment, one notes that the six fundamental requirements for the acceptability of a historical trial proposed by Pocock are not met by the three selected historical controls, Hamstra, Fishbane, and Feridex.

As this reviewer mentioned in the sub-section of Comment on issue I, the major problem with historical controls is that one is unable to ensure comparability between the groups of patients and methods of evaluation for the new and standard treatment. In addition, Fleming emphasized in his paper entitled "Historical controls, data banks, and randomized trials in clinical research: A review", published by Cancer treatment reports Vol. 66, No. 5, pp. 1101-1105, May 1982, that the property of unbiasedness, particularly in the elimination of systematic dissimilarities that occur among treatment groups and that are caused by unknown or unrecorded prognostic factors, is a fundamental component to a fair, reliable, and reproducible evaluation of treatment.

Therefore, in order to eradicate the bias induced by the historical control trials and meet the regulatory standard as depicted in the section of Comment on issue I,

(For more detail on the inadequacy of the selected control studies, refer to the medical reviewer's report.)

Comment on Issue III - The issue on the identification of all (drug) allergic event.

This reviewer therefore, would like to comment on the two issues below with regard to the identification of all allergic events (suspected and confirmed) for both Ferrlecit and placebo:

- As noted in Volume 38.5 submitted by the sponsor, the rate of all (drug) allergic events for Ferrlecit was to be declared POSITIVE to that of placebo if the rate of all allergic reactions to Ferrlecit was either significantly less than or statistically indistinguishable from that of placebo. Since the POSITIVE comparison result on the all allergic events for Ferrlecit versus placebo, it can be achieved by identifying approximately equal drug allergic events between Ferrlecit and placebo.

- As noted in Volume 38.5 submitted by the sponsor, patients participated in the study were randomized to one of the two crossover treatment schedules: 1.) Ferrlecit at the secondary hemodialysis section (HD#2) and placebo at HD#3 or 2.) placebo at HD#2 and Ferrlecit at HD#3. By the analysis theory of the cross over design, the carry over effect of one treatment to another is confounded with the treatment effect/safety comparisons and is therefore, always received a great attention. In addition, one notes that the sponsor only provided two days for drug wash out period. Unless the sponsor can justify, from medical expertise, that the carry over effect can be ignored, the two days wash out period may be not long enough for the carry over effect of Ferrlecit being eliminated. It follows that the allergic events identified for the placebo patients who were assigned to the first crossover treatment schedule, Ferrlecit at HD#2 (first) and placebo at HD#3 (second), were considered confounded with the effect of Ferrlecit.

Comment on issue IV – The statistical analysis on the primary adverse events

i. Issue on the validity of the interim analysis

As we note from this NDA submission, the results for the safety comparisons on life-threatening, drug intolerance, and drug allergic events among the three treatment groups, Ferrlecit, iron dextran, and placebo, reported by the sponsor, were from an interim analysis. In order to achieve a pre-specified Type I error rate (for example 0.05) and a valid statistical analysis results, before conducting the trial, the sponsor should apply group sequential method to plan the nominal significance level and the type of group sequential boundary (for example: Pocock or O'Brien) used at each stage of interim analysis.

However, it is noted that before conducting the NDA study, the sponsor did not set up a plan for the interim analysis to specify the type of group sequential boundary being used and the number of interim looks to control the pre-specified .05 Type I error rate. Therefore, under the situation of no interim plan, after unblinding data, no method can be used to unbiasedly control the pre-specified .05 Type I error rate. It follows that the results from the interim analyses are questionable.

ii. Issue on the statistical distributions for the primary adverse events

As noted by this reviewer on the issues of inadequate selections for the three historical trials, the demographics and baseline characteristics (for example: the criteria on the assessment of adverse event and the selection of patient population, and dosage, ..., etc.) were considerably different between historical controls (Hamstra, Fishbane, and Feridex) and concurrent study FER 9803. Therefore, no statistical distributions can be used to perform the statistical analysis for the comparisons between iron dextran and Ferrlecit on the two primary adverse events: life-threatening and drug intolerance. It follows that the analysis results on the life threatening and drug intolerance events presented in Table 2.2.1, performed by the sponsor are not correct.

As to the all (drug) allergic events, the analysis results on the all (drug) allergic events, performed by the sponsor, presented in Table 2.2.1 are not reliable due to the following two factors:

- The two issues, the bias identification on this adverse event and the carry over effect of Ferrlecit noted by the section of Comment on Issue III, provide considerably bias in favor of Ferrlecit when examining the drug allergic events. Therefore, no valid binomial distributions can be applied to compare the drug allergic events between placebo and Ferrlecit.
- In the protocol, the sponsor indicated that the total sample size 2409 for the Ferrlecit group was determined by a two sided test with 80% power assessed by the alternative hypothesis with 2.78% iron dextran event rate and 1.60% Ferrlecit event rate following a parallel group design. However, the difference of all allergic event rates between Ferrlecit and placebo compared by McNemar test specified by the sponsor in the protocol stage was using data from a cross over design. In order to avoid lack of power to detect the pre-specified size of the all allergic event rate difference between Ferrlecit and placebo, the power for the McNemar test should be assessed using the cross over design. However, even under the situation of lacking power, using the per-protocol population data (from the interim analysis) submitted by the sponsor on 12/12/2000, the null hypothesis that the rate of Ferrlecit suspected allergic reactions is either significantly less than or statistically indistinguishable from that of placebo is borderline rejected (the one-sided exact p-value for the McNemar's method equal to 0.035, close to .025 one sided significance level), indicating that the rate of suspected reactions to Ferrlecit was borderline significantly higher than that of placebo.

2.4 Overall Conclusions

- In order to eradicate the bias induced by the historical control trials and meet the regulatory standard as depicted in the section of Comment on issue I, in this treatment safety comparisons,
- Beside showing the rate of all (drug) allergic reactions to Ferrlecit either significantly less than or statistically indistinguishable from that of placebo,
- No statistical distributions can be used to perform the statistical analysis for the comparisons between iron dextran and Ferrlecit on the two primary adverse events: life-threatening and drug intolerance. It follows that the analysis results on the life threatening and drug intolerance events presented in Table 2.2.1, performed by the sponsor, are not valid.
- No valid binomial distributions can be applied to compare the all (drug) allergic events between placebo and Ferrlecit. In addition, It may be lack of power for McNemar test to detect the pre-specified size of the all (drug) allergic event rate difference between Ferrlecit

and placebo. It follows that the analysis results on the all (drug) allergic events presented in Table 2.2.1 by the sponsor are not reliable.

➢ One notes that the primary analyses are failed to support the primary objective, [redacted]

Therefore, no type I error rate left for the secondary analyses, including the logistic regression analyses on concomitant angiotensin converting enzyme inhibitor therapy and on prior iron dextran exposure, to be reviewed.

Wen-Jen Chen Ph.D.,
Mathematical Statistician

Concur: Dr. Permutt

cc: Archival NDA# 20-955
HFD-180 Div File
HFD-180/Dr. Talarico
HFD-180/Dr. Lu
HFD-180/Ms. Strongin
HFD-715/Dr. Nevius
HFD-715/Dr. Permutt
HFD-715/Dr. Chen
HFD-715/File Copy

This file is stored in "c:\wdreview\felsup.doc".

/s/

Wen-Jen Chen
1/8/01 04:01:59 PM
BIOMETRICS

Thomas Permutt
1/9/01 11:10:32 AM
BIOMETRICS
concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-955/S-003

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA: 29-955 / SE8-003 **Stamp Date**: 8/2/00

Active Ingredient: Ferric Sodium Gluconate Complex in Sucrose Injection

Trade Name: Ferrlecit

Sponsor: R&D laboratories, Inc.

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Type of Submission: Population PK Study report & Labeling Amendments

Background

Ferrlecit is a macromolecular complex with an apparent molecular weight of 350,000 ± 23,000 D. The complex is formed by chelation of gluconate molecules to ferric ions. Ferrlecit was first marketed in 1959 in Germany as an intravenous iron complex for the management of recalcitrant iron deficiency anemia.

Each ampule of 5 ml Ferrlecit for I.V. 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) in water for injection, pH 7.7-9.7. Each ml also contains 9 mg of benzyl alcohol as an inactive ingredient.

Ferrlecit was submitted to the Agency on June 30, 1998 as an injectable iron formulation for first-line treatment for iron-deficiency in renal hemodialysis patients on supplemental recombinant human erythropoietin. It was deemed to be approvable pending several additional studies in the post-marketing phase.

In the current submission, the firm proposes amendments to the Clinical Pharmacology and Biopharmaceutics section of Ferrlecit labeling based on the results of a single-dose pharmacokinetic study (FER9801). Study FER9801 is entitled, "Open –Label, Dose Ranging Study to Determine the Single-Dose Pharmacokinetics of Ferrlecit® Following Intravenous Administration to Healthy, Iron Deficient Volunteers".

Study FER9801 evaluated the pharmacokinetics of 4 Ferrlecit I.V. infusion regimens: Regimen A (62.5 mg over 30 min), Regimen B (125 mg over 60 min), Regimen C (62.5 mg over 4 min) and Regimen D (125 mg over 7 min). (A detailed description of the study design is included in CPB review dated 4/27/99).

The objectives of study FER9801 were:

1. To confirm existing single dose pharmacokinetic data on the primary PK parameters for Ferrlecit.
2. To compare the single dose pharmacokinetics of a rapid administration regimen (20 mg/min) to that used in the clinical studies (2.1 mg/min).
3. To study immediate changes in iron storage parameters as % transferrin saturation and serum apoferritin, in the first 72 hours following drug administration.

The Ferrlecit-bound iron (FBI) and transferrin-bound iron (TBI) concentrations obtained from study FER9801 were simultaneously fitted to a compartmental pharmacokinetic model (Fig. 1) using nonlinear-mixed-effects modeling (NonMem)[1]. The assumptions utilized during the pharmacokinetic model building stage included:

- Less than 2% of Ferrlecit is excreted renally, thus the renal route of elimination was assumed to have a negligible contribution to the total Ferrlecit clearance.
- Ferrlecit was assumed to deliver iron mainly to the reticuloendothelial system (RES).
- Unidirectional delivery from RES to the storage compartment was assumed, as it is thought that delivery of iron from the RES to the storage compartment is primarily through transferrin.

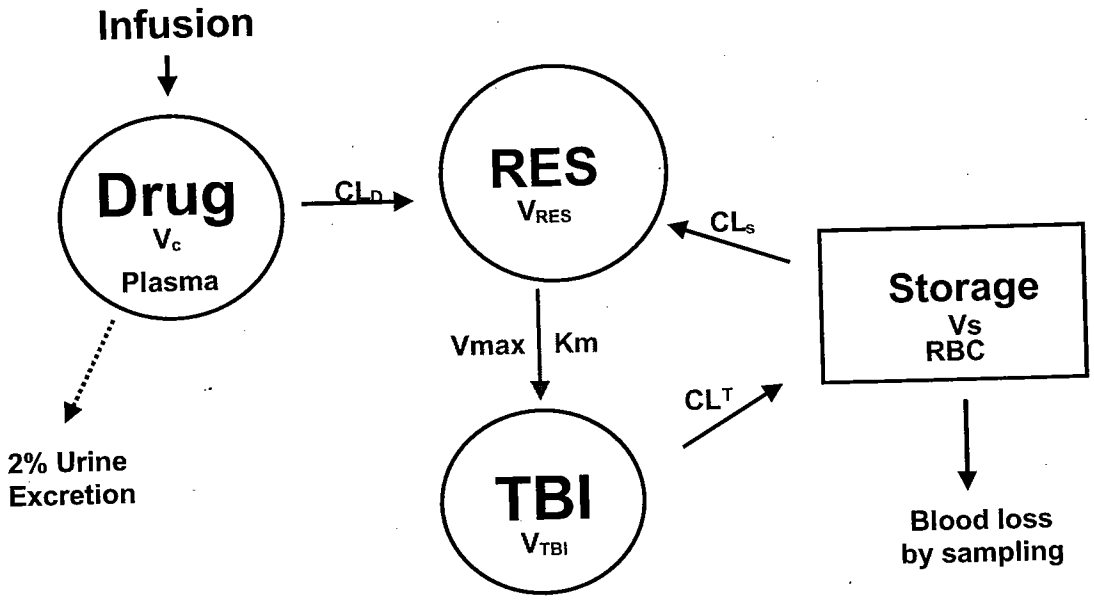


Fig. 1. Iron movement model after administration of Ferrlecit until 72 hours.

[1] See attachment 1 for a detailed report on the population PK analysis methods and results.

Results

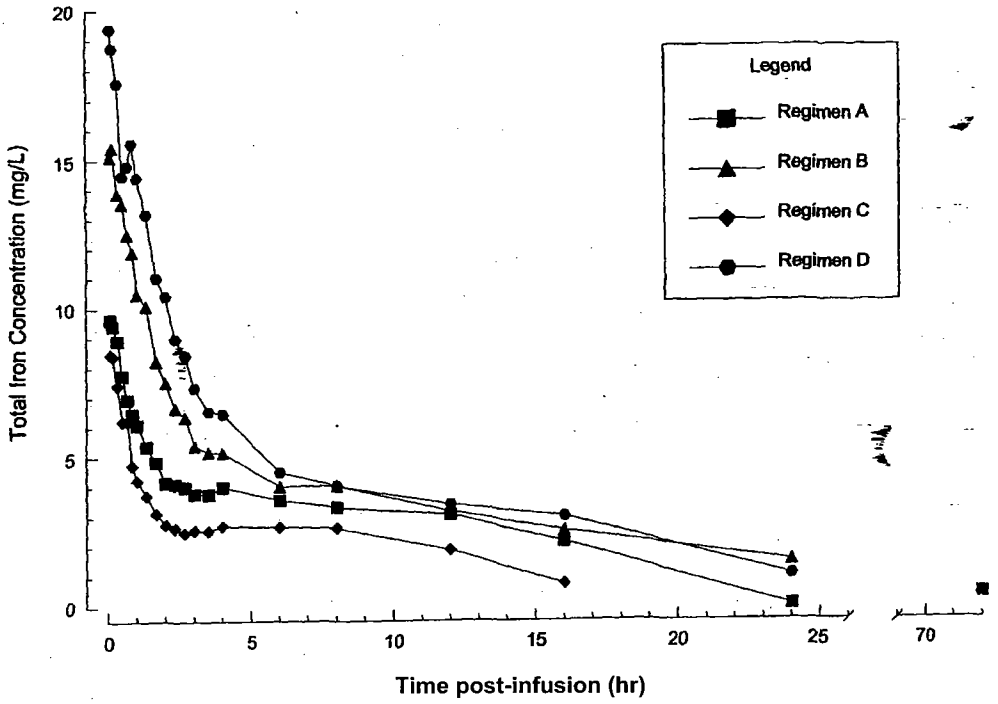


Fig. 2. Mean total iron concentration in serum over time.

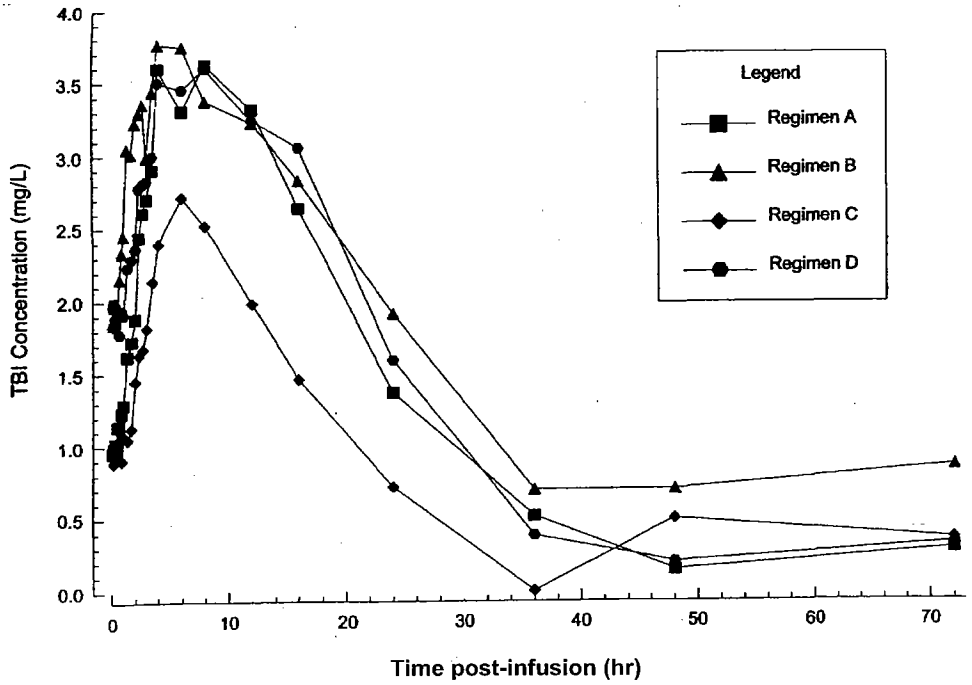


Fig. 3. Mean TBI concentration in serum over time.

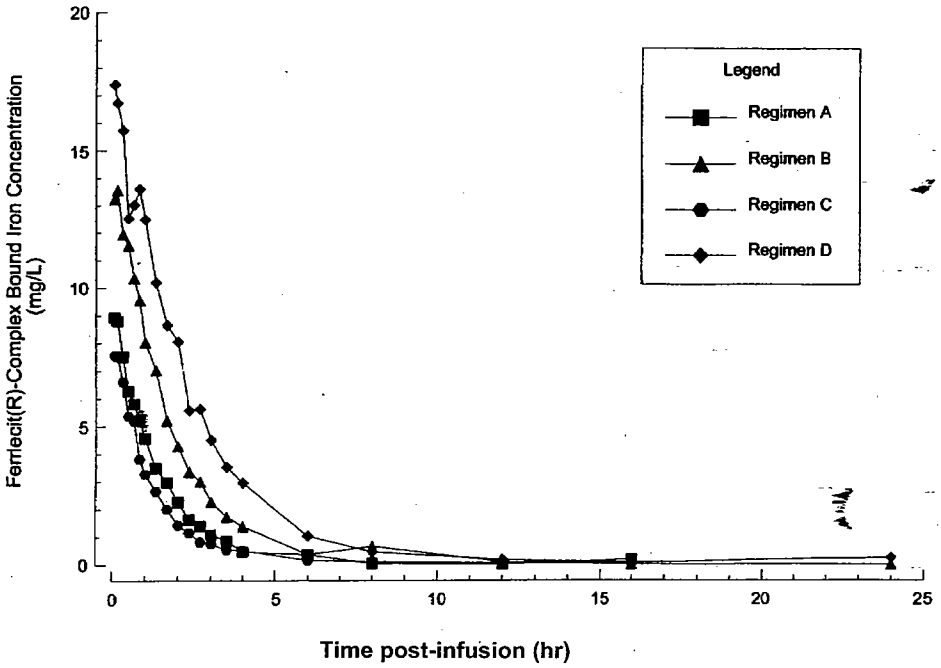


Fig. 4. Mean FBI concentration in serum over time.

- Earlier publications hypothesized that a fraction of the iron molecules in Ferrlecit may be free, and hence, may be available for direct binding to transferrin. The analysis indicates that delivery of iron from Ferrlecit-bound iron to transferrin without first being processed by the RES is relatively small (0.1 L/hr) compared to transfer of iron from Ferrlecit-bound iron to the RES (3.76 L/hr).

- The analysis also indicates that when the available iron in the RES is low, iron is delivered to transferrin in a linear manner. At high RES iron concentrations, the delivery rate reaches a plateau with a maximum rate of delivery (Vmax). Thus, the delivery of iron from the RES to transferrin seems to be saturable following Michaelis-Menten kinetics.

- Several covariates including age, sex, weight, height, body mass index, ferritin, blood urea nitrogen and albumin concentrations were examined for their contribution to inter-individual variability. However, none of the covariates examined had a significant effect.

Table 1. Parameter Estimates and Variabilities for Population PK Model of Ferrlecit

Parameter	Symbol*	Parameter Estimate	Standard Error (%)
Iron delivery rate from Ferrlecit to RES (L/hr)	*CL1*	3.76	8.0
Interindividual variability in CL1 (%)	*cvCL1*	30	44.1
Volume of distribution in serum (L)	*V1*	6.30	3.6
Iron delivery maximum rate from RES to transferrin (mg/hr)	*Vmax*	9.11	18.4
Concentration at 50% of Vmax (mg/L)	*Km*	3.85	35.8
Volume of distribution in RES (L)	*VRES*	14.6	23.2
Iron delivery rate from transferrin to storage (L/hr)	*CLT*	1.84	13.4
Interindividual variability in CLT (%)	*cvCLT*	35	42.6
Iron delivery rate from storage to RES (L/hr)	*CLS*	0.000001 fixed	NA
Volume of distribution in transferrin (L)	*VTBI*	3.04	20.4
Interindividual variability in VTBI (%)	*cvVTBI*	17	62.4
Baseline TBI concentration (mg/L)	*TBI0*	0.78	11.0
Interindividual variability in TBI0 (%)	*CvTBI0*	40	41.3
Additive Residual Error for DBI (SD, mg/L)	*Dadd*	0.60	15.2
Proportional Residual Error (CV, %)	*Dpro*	21	9.8
Additive Residual Error for TBI (SD, mg/L)	*Tadd*	0.34	6.3

Reviewer's Recommendations

The population PK analysis for study FER9801 has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/Division of Pharmaceutical Evaluation II), and from the view point of OCPB, the submitted population PK analysis is found to be acceptable. See attachment 2 for the final version of the **Clinical Pharmacology** section of Ferrlecit labeling.

Suliman I. Al-Fayoumi, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Suresh Doddapaneni, Ph.D., Team Leader _____

cc: HFD-180: NDA 20-955 (1x); DIV FILE (1x); BSTRONGIN (1x); SDODDAPANENI (1x); SALFAYOUMI (1x); HFD-870: HMALINOWSKI (1x); CDR: ATTN ZOM ZADENG

Attachment 1

R&D Ferrlecit® Pharmacokinetic Modeling Report

Protocol No. FER9801

IND No. 47764

December 11, 2000

Reported by

Hui Kimko, PhD

Table of Contents

List of Tables and Figures

A. List of Tables

B. List of Figures

C. List of Figures (Appendix)

List of Abbreviations Used in This Report

DBI	Drug Bound Iron
TBI	Transferrin Bound Iron
CL1	Iron delivery rate from Ferrlecit to RES
cvCL1	Interindividual variability in CL1
V1	Volume of distribution in serum
Vmax	Iron delivery maximum rate from RES to transferrin
cvVM	Interindividual variability in Vmax
Km	Concentration at 50% of Vmax
cvKm	Interindividual variability in Km
VRES	Volume of distribution in RES
CLT	Iron delivery rate from transferrin to storage
cvCLT	Interindividual variability in CLT
CLS	Iron delivery rate from storage to RES
VTBI	Volume of distribution in transferrin
cvVTBI	Interindividual variability in VTBI
TBI0	Baseline TBI concentration
CvTBI0	Interindividual variability in TBI0
Dadd	Additive Residual Error for DBI
Dpro	Proportional Residual Error for DBI
Tadd	Additive Residual Error for TBI
Tpro	Proportional Residual Error for TBI
BMI	Body Mass Index (Kg/m^2)
RES	Reticuloendothelial system
CL_R	Linear clearance of iron from RES to transferrin
CV	Coefficient of Variation (%)
FO	First Order Method
FOCE	First Order Conditional Estimation Method
PK	Pharmacokinetic(s)
PD	Pharmacodynamic(s)
SE	Standard Error

Introduction

Ferrlecit® is sodium ferric gluconate complex in sucrose injection, whose indication is for iron deficiency in the hemodialysis patient receiving erythropoietin therapy. It is a stable macromolecular complex with an apparent molecular weight of 350,000 ± 23,000 daltons. Since gluconate chelates to ferric ions with a binding coefficient of 10^3, the resulting complex is likely to be relatively stable in serum until the complex is endocytosed into reticulo-endothelial cells. Release of iron (III) from Ferrlecit® to transferrin is postulated based on the much higher binding coefficient of transferrin (10^{23}).

R&D Laboratories performed a single-center, open-label, dose-ranging study to determine the single-dose pharmacokinetics (PK) of Ferrlecit®. The objectives of the study were

- To confirm existing single dose kinetic data on the half-life, volume of distribution and area under the curve for the iron complex identified as Ferrlecit®.
- To compare the single dose kinetics of more rapid administration (20 mg/min) to that which was used in clinical studies in the United States (2.1 mg/min)
- To study immediate changes in classical iron storage parameters [percent (%) transferrin saturation and serum apoferritin] in the first 72 hours following drug administration.

This report is to summarize the population PK analysis methods and results. This analysis was conducted using the nonlinear mixed-effects modeling approach.

Objectives

The objectives of this population PK analysis are:

- To characterize the PK profiles based on the understanding of physiology and pharmacology;
- To quantify important population PK parameters and their variabilities, including interindividual and residual (intraindividual) variabilities; and,
- To identify significant and meaningful covariates which might influence population PK parameters and/or their variabilities.

Materials and Methods

3.1 Study and Patients

This was a single-center, open-label, randomized study to determine the PK of Ferrlecit® in iron deficient adult volunteers following four different single dose intravenous infusions. Subjects were randomly assigned to one of two dosing regimens (A or B), then, in a second study phase, re-randomized to one of two additional dosing regimens (C or D).

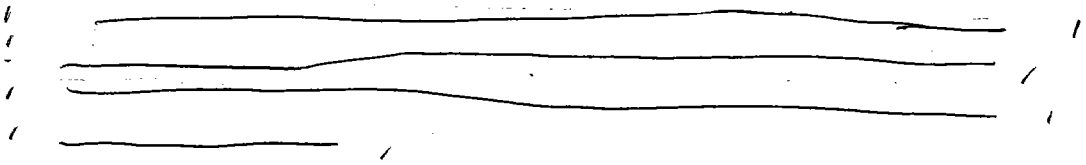
- Regimen A: 62.5 mg dose (1 ampule) administered undiluted by syringe pump as a single intravenous infusion over a period of 30 minutes

- Regimen B: 125 mg dose (2 ampules) administered undiluted by syringe pump as a single intravenous infusion over a period of 60 minutes
- Regimen C: 62.5 mg dose (1 ampule) administered undiluted by syringe pump as a single intravenous infusion over a period of 4 minutes
- Regimen D: 125 mg dose (2 ampules) administered undiluted by syringe pump as a single intravenous infusion over a period of 7 minutes

A total of 14 male and female volunteers were enrolled in, and completed, the study. The summary of covariates (demography and chemistry) is in Table 1. For this study, written informed consent was obtained from all patients. All studies were approved by independent ethics committees or institutional review boards, and conducted according to current Good Clinical Practice and other applicable regulatory requirements.

In contrast to earlier studies of single dose intravenous infusion of iron complexes, for this study, [redacted] assays were developed. Previous research had established that, after exogenous iron administration, laboratory assay of endogenous serum transferrin bound iron (TBI) was fraught with error. The error was induced by the technique of using a strong reducing agent and simultaneous acidification of the serum sample. These methods result in variable destruction of exogenous serum iron complexes, including either iron dextran or sodium ferric gluconate complex, with release of iron into the serum sample, which is then falsely measured as if this iron were transferrin bound iron. [redacted]

Blood samples for measurements of total iron and TBI in serum were collected at the following times relative to the end of the infusion: 5, 10, 20, 30, 40, 50 minutes and 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, 48, 72 hours. Sample sizes were 5 mL of whole blood at most times except for sample sizes of 15mL at –24, 0, 24, 48, and 72 hours and 12 mL at 2, 4, 6, 8, and 16 hours. [redacted]



3.2 Construction of Data Sets

In the population PK analysis, the data from one occasion of subject 4 (Regimen C) was excluded because of an erratic PK profile that reflects problems either in sample collection or assay. The covariates were included in the data set to evaluate the effects of covariates such as gender, age, sex, weight, height, body mass index, ferritin, blood urea nitrogen, and albumin concentrations. The data set used in the model building process includes [redacted] concentrations and [redacted] concentrations.

3.3 Data analysis Method

Nonlinear mixed-effects modeling is well suited to handle population PK data because it is possible to simultaneously quantify fixed effects and random effects such as interindividual, and residual or intraindividual variability. Differences in the timing and number of observations between subjects can be also easily handled.

3.4 Model Building

Based on understanding of iron movement in the body, a structural model was hypothesized as shown in Figure 1. Since less than 5% of Ferrlecit was excreted renally, this renal path was not accounted in the model. Ferrlecit was assumed to deliver iron mainly to the reticuloendothelial system (RES). The direct delivery of iron to TBI was tested. The iron distributed to TBI goes to the storage compartment such as red blood cells and ferritin, from which iron is eventually released. Since it is known that delivery of iron from the RES to the storage is mainly through transferrin, unidirectional delivery from RES to the storage through transferrin was assumed.

3.3.1 General Procedures

The DBI and TBI concentrations were simultaneously fitted. All analyses were carried out with NONMEM (University of California, San Francisco) and Digital Fortran (version 6, MicroSoft). The parameters that require estimation of interindividual variability (IIV) were searched using First Order (FO) option. For covariate search, the FO method was also used. In order to obtain the final parameter estimates, the First Order Conditional Estimation (FOCE) method with Interaction options were used. Of all models explored and tested, the key models are described in this report.

3.3.2 Model Development Strategy

First, a basic structural PD model with interindividual variability was built using the FO method of NONMEM. All the PK parameters were subjected to IIV initially, but IIV for each parameter was dropped step by step to test its statistical significance. The correlation between parameters were also explored using OMEGA BLOCK in the NONMEM. To do so, individual *post hoc* values for one parameter variability were plotted against values for other parameter variability. Once a plausible correlation between two or more variability values was found, it was modeled and tested. The inclusion criterion of inter-individual variability was that the objective function value should decrease by as much as 10.8 at the alpha error level of 0.1% with degree of freedom of 1.

For a significant covariate(s) search, autocovariate function (NMAC command) of Wings for Nonmem (http://www.geocities.com/wfn2k/index.htm) was used. The decision to include a covariate in the model was based on a statistical criterion. By default, this was a change in objective function of 3.84 units or greater. When adding a covariate does not decrease the objective function by more than 3.84 units, backward elimination was performed. Each of the covariates in the full model was removed one at a time with replacement. The default statistical criterion for backward elimination was a change in objective function of 10.83.

During the whole process of model development, graphical methods were also employed to judge general goodness-of-fit. Plots of observed versus model-based population or individual *post hoc* predicted values, and various residual plots were used to detect any significant systemic departure from the model assumptions (homogeneity of variance or heteroscedasticity, normality or log-normality, homogenous residual plots, etc.).

3.3.3 Modeling Stochastic Variability

3.3.3.1 *Population Parameter Variability*

We assumed that interindividual variability is log-normally distributed. This assumption is described in the following equation where θ_{ki} is the kth parameter of the ith individual, θ_k is the model-based typical value (population mean) for the kth parameter, and $\exp(PPV_{ki})$ is the random difference between θ_{ki} and θ_k. Population parameter variability, $PPV_i = (PPV_{1i}, PPV_{2i}, \ldots, PPV_{mi})$, was assumed to be independent multivariate normally distributed, with mean 0 and with variance - covariance matrix Ω with diagonal elements $(\omega_1^2, \omega_2^2, \ldots, \omega_m^2)$ such that the ω_k is approximately the coefficient of variation of kth parameter with respect to the typical value, θ_k.

$$\theta_{ki} = \theta_k \cdot \exp(PPV_{ki})$$

3.3.3.2 ***Residual Errors***

The combined additive and proportional random error model was used to explain residual error or intraindividual variability for the DBI and TBI measurements. This is described in the following equation where $Iron_{obs,\,it}$ is an observed iron concentration value for the *i*th individual measure at the time *t, and* $Iron_{it}$ is a model based individual *post hoc* predicted value for the same individual at the same time. An additive random error ($\varepsilon_{it,\,a}$) was assumed to be independent normally distributed with mean of 0 and variance σ^2, and a proportional random error ($\varepsilon_{it,\,p}$) was assumed to be independent log-normally distributed.

$$Iron_{obs,it} = Iron_{it}\,(1 + \varepsilon_{it,\,p}) + \varepsilon_{it,\,a}$$

Precision

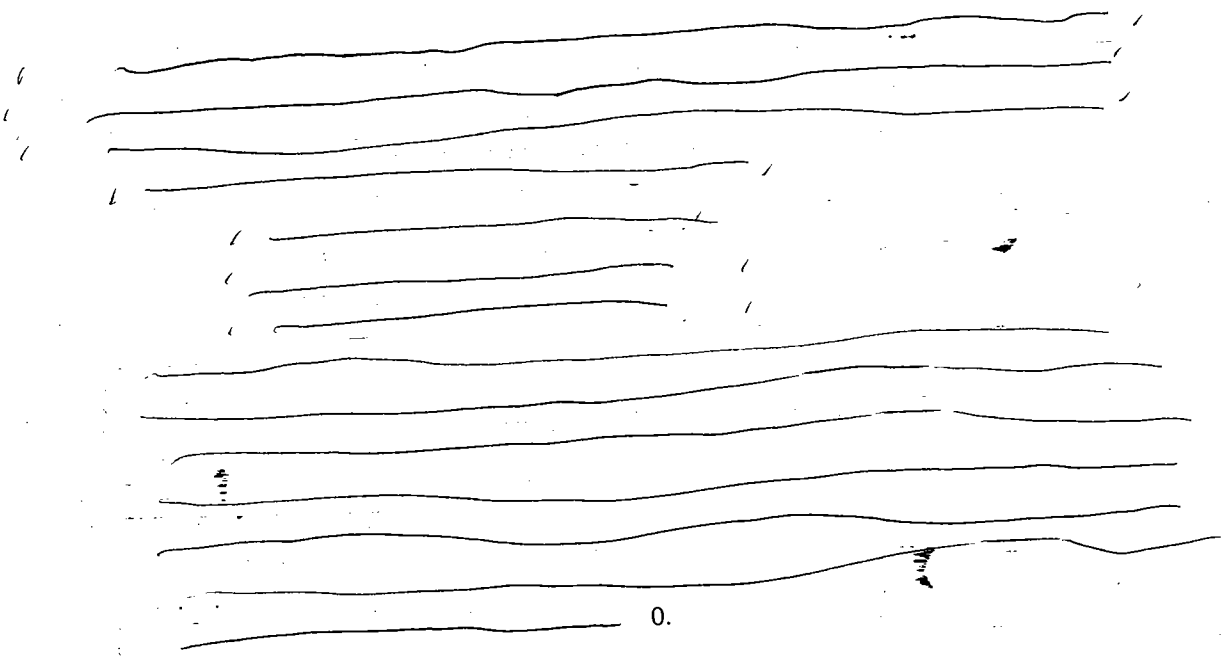
The precision (standard error) of the estimated parameters was obtained by NONMEM FOCE INTERACTION method.

Results

4.1 Base Structural Model

Based on understanding of the movement path of iron, four compartments were used to describe the observed time courses of DBI and TBI. Linear first order rates were assumed for the pathways between (a) serum and RES (CL_D), (b) RES and TBI (CL_R), (c) TBI and Storage (CL_T), and (d) Storage and RES (CL_S). However, nonlinear rate assumption of the pathway between RES and TBI yielded better fit (objective function value decreased by 82), which implies iron is delivered to transferrin at a nonlinear saturation rate. Therefore, a model was developed with the nonlinearity assumption in this delivery pathway (Run b00lin.lst in Appendix IV).

The volume of storage was not estimated because there was insufficient information to estimate it from two measured variables, DBI and TBI concentrations. Additionally, as the delivery rate from the storage compartment (CL_S) was negligible, the total delivered iron amount per unit time would not affect the net rate change in iron delivery in the storage compartment.



4.2 Interindividual Variability

The clearances from the drug to RES and from transferrin to storage, volume of distribution of transferrin, and baseline TBI concentrations had statistically significant interindividual variability at the alpha level of 0.01. Therefore, the final model explains the variabilities among subjects by allowing variabilities in the parameter estimates.

4.3 Effect of Covariates

Figure 2 summarizes distribution of covariates considered in the model development process, although the number of subjects (14) is not sufficient to represent in histograms. Even with total of 14 subjects, the covariates were distributed more or less widely. Although the number of subjects was small, covariate search was performed. Stepwise forward and backward covariate search was performed using the Autocovariate search program in the Wings for Nonmem. The control stream is shown in Appendix II. No covariate was found to be significant in explaining interindividual variability. This covariate search was performed using FO option, because FOCE option tended to yield similar estimates in the model building processes with this data set, and was not efficient and yielded numerical errors.

4.4 Final Model

The four compartment model shown in Figure 1 characterized the PK profiles of DBI and TBI well. The basic diagnostic plots are in Figure 2, and the individual fits are shown in Figure 3. The estimated parameters are in Table 1.

Discussion

Population approach was used to characterize the PK profiles of drug bound iron and transferrin bound iron. The standard two-stage (STS) method is computationally simple, but the method does not take into account the uncertainty in estimating the individual specific variability and gives biased estimates of population variances of parameters. Therefore, the STS method is not generally recommended.

Ferrlecit® delivers iron mainly to the reticuloendothelial system. Less than 5% of Ferrlecit® is excreted renally. Delivery of iron from DBI directly to transferrin without first being processed in the RES was estimated negligible (10^{-6} L/hr) compared to the pathway from the DBI to the RES (3.76 L/hr) as shown in the Nonmem run, d22cl2ce.lst, in the Appendix IV. These data support the postulation that the degradation of the high molecular weight complex found in sodium ferric gluconate by the RES is required before individual iron can be released to transferrin. In contrast, prior publications have hypothesized that some iron molecules in Ferrlecit may, in fact, be "free" and thus available for direct transfer to transferrin. While this postulation is not supported by the known chemistry of Ferrlecit, this study has shown this alternative metabolic pathway to be minor. Therefore, the direct delivery to transferrin and renal excretion were regarded as negligible, and not included in the model building process.

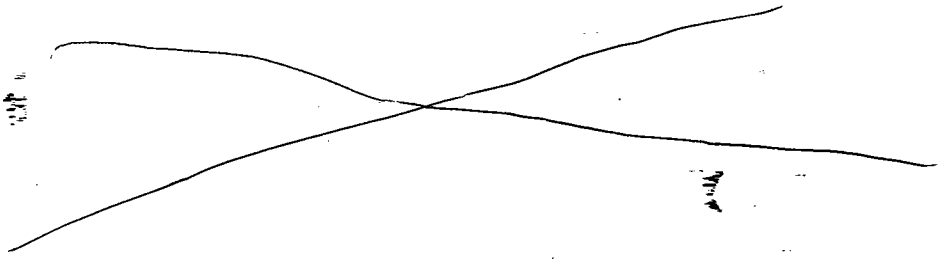
The delivery of iron from the RES to transferrin was saturated following Michaelis-Menten kinetics. When the available iron in the RES is low, iron was delivered linearly, and at a high iron concentration the delivery rate reached a plateau with a maximum rate of delivery (Vmax) of [redacted] This value agrees with the finding from the other investigators using different methods (Hamstra RD, Block MH, Schocket AL. Intravenous Iron Dextran in Clinical Medicine. JAMA 243:1726-1731, 1980). The iron concentration at the half of Vmax was estimated to be [redacted]. Physiologically, therefore, iron delivery to the bone marrow and red blood cells is limited by the transferrin carrying capacity which, when saturated, precludes further release of iron from the RES.

The volume of distribution for the RES was estimated to 14.6 L (SE 23.2 %). This corresponds well to typical physiological estimates of total volume of the reticuloendothelial system in man.

The iron delivery from the RBC to the RES (CLs) was estimated to be negligible ($<10^{-6}$). This agrees well with the fact that in this study the pool of RBC is mainly composed of young RBCs produced from the supply of iron introduced. In order to allow circulation of iron back to the RES from the senescent RBC and to avoid numerical problem, the CLs was fixed to 10^{-6}. The loss of iron by blood sampling was also considered in the data analysis. It was assumed that it took 30

seconds to withdraw blood, and hematocrit was used to calculate the amount of iron lost in the measured volume.

Age, sex, weight, height, body mass index, ferritin, blood urea nitrogen, and albumin concentrations were tested if the differences in these covariates in the subject population caused the interindividual variability shown in Table 1. However, no covariate was found significant.



Conclusion

The final 4 compartment model characterized the time courses of measured DBI and TBI concentration well.

Tables & Figures

List of Tables

List of Figures

Table 2. Parameter Estimates and Variabilities for Population PK Model of Ferrlecit

Parameter	Symbol*	Parameter Estimate	Standard Error (%)
Iron delivery rate from Ferrlecit to RES (L/hr)	*CL1*	3.76	8.0
Interindividual variability in CL1 (%)	*cvCL1*	30	44.1
Volume of distribution in serum (L)	*V1*	6.30	3.6
Iron delivery maximum rate from RES to transferrin (mg/hr)	*Vmax*	9.11	18.4
Concentration at 50% of Vmax (mg/L)	*Km*	3.85	35.8
Volume of distribution in RES (L)	*VRES*	14.6	23.2
Iron delivery rate from transferrin to storage (L/hr)	*CLT*	1.84	13.4
Interindividual variability in CLT (%)	*cvCLT*	35	42.6
Iron delivery rate from storage to RES (L/hr)	*CLS*	0.000001 fixed	NA
Volume of distribution in transferrin (L)	*VTBI*	3.04	20.4
Interindividual variability in VTBI (%)	*cvVTBI*	17	62.4
Baseline TBI concentration (mg/L)	*TBI0*	0.78	11.0
Interindividual variability in TBI0 (%)	*CvTBI0*	40	41.3
Additive Residual Error for DBI (SD, mg/L)	*Dadd*	0.60	15.2
Proportional Residual Error (CV, %)	*Dpro*	21	9.8
Additive Residual Error for TBI (SD, mg/L)	*Tadd*	0.34	6.3

Figure 1. *Iron movement model after administration of Ferrlecit® until 72 hours*

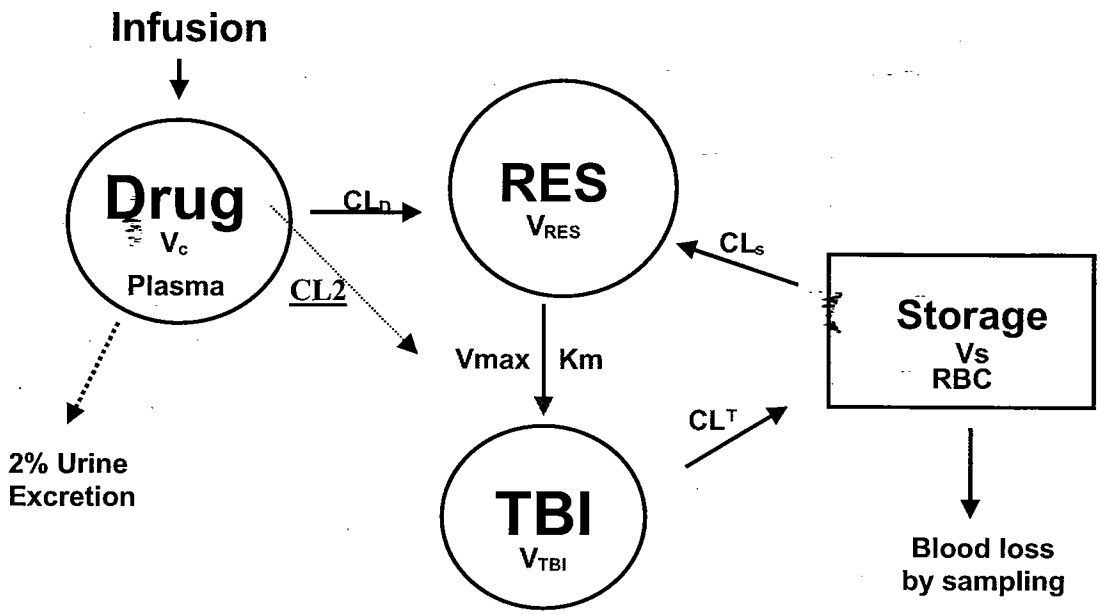
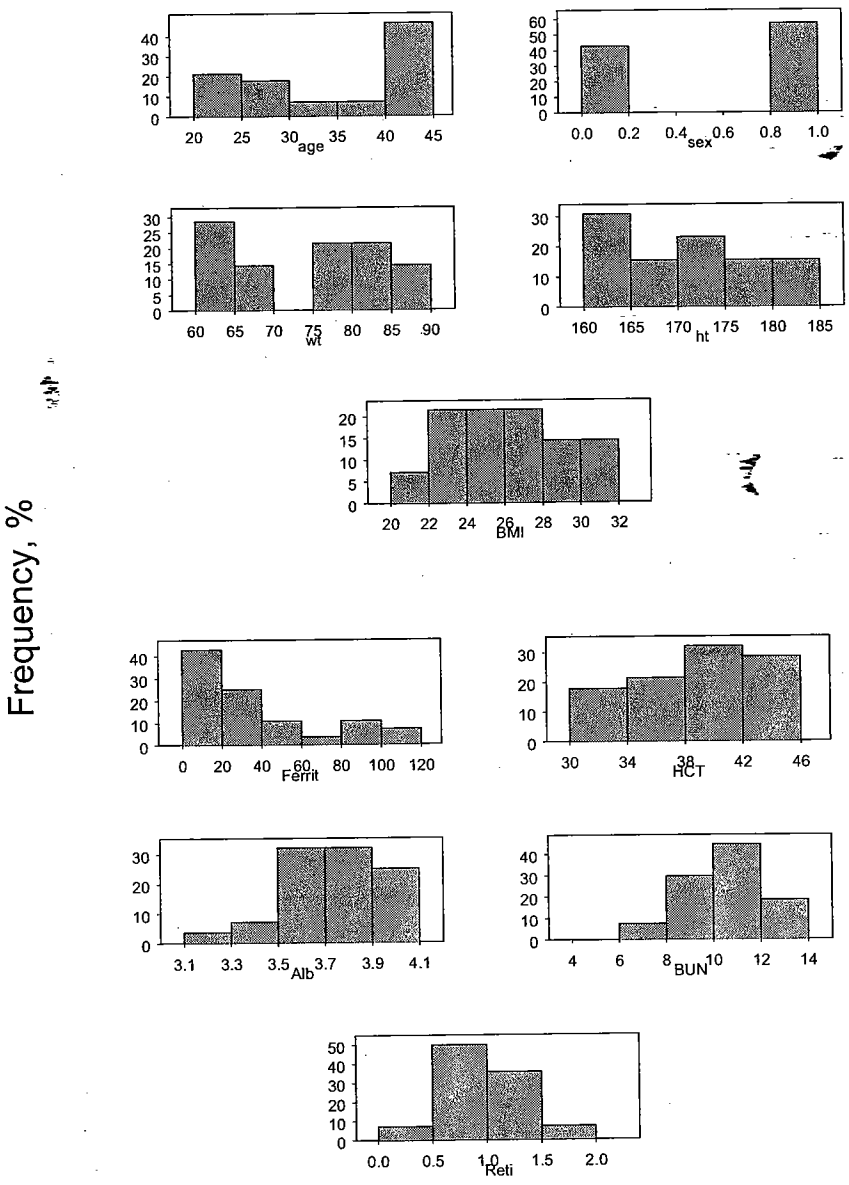


Figure 2. *Distributions of covariates*



14 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 20-955 S003

Attachment 2

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 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 (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 can include 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 epoetin dosage with stable hemoglobin/hematocrit when parenteral iron is administered.

Pharmacokinetics

Multiple sequential single dose intravenous pharmacokinetic studies were performed on 14 healthy iron-deficient volunteers. Entry criteria included / In the 1st stage, each subject was randomized 1:1 to undiluted Ferrlecit® injection of either 125 mg/hr or 62.5 mg/½ hr (2.1 mg/min). Five days after the 1st 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 (C_{max}) varied significantly by dosage and by rate of administration with the highest C_{max} observed in the regimen in which 125 mg was administered in 7 minutes (19.0 mg/L). The initial volume of distribution (V_{Ferr}) of 6 L corresponds well to calculated blood volume. V_{Ferr} did not vary by dosage or rate of administration. The terminal elimination half-life ($_z$-HL) for drug bound iron was approximately 1 hour. $_z$-HL varied by dose but not by rate of administration. The shortest value (0.85 h) occurred in the 62.5 mg/4 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 17.5mg-h/L (62.5 mg) to 35.5 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 ionic 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.

In vitro experiments have shown that less than 1% of the iron species within Ferrlecit® can be dialyzed through membranes with pore sizes corresponding to 12,000 to 14,000 daltons over a period of up to 270 minutes. Human studies in renally competent subjects 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.

/s/

Suliman Alfayoumi
1/31/01 12:53:02 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
1/31/01 12:59:59 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-955/ S-003

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

EXCLUSIVITY SUMMARY for NDA # 20-955 SUPPL # SE8-003
Trade Name Ferrlecit® Generic Name sodium ferric gluconate complex in sucrose injection
Applicant Name R & D Laboratories, Inc. HFD- 180
Approval Date 2/2/01

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X/

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE8

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /___/ NO /_X_/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The labeling changes in S-003 were based on an interim analysis of Study FER 9803, "Crossover, Randomized, Blinded, Prospective, Multicenter Clinical Evaluation of the Rate of Adverse Events to Ferrlecit® in Hemodialysis Patients as Compared to Placebo and Historical Controls" and Study FER9801, "Open-Label, Dose Ranging Study to Determine the Single-Dose Pharmacokinetics of Ferrlecit® Following Intravenous Administration to Healthy, Iron Deficient Volunteers". Study FER 9803 was performed in response to a Phase IV commitment to "provide additional safety data". Study FER 9801 was performed in response to a Phase IV commitment to, "conduct a pilot human PK study".

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

N/A

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /_X_/ NO /___/

If yes, NDA # 20-955 Drug Name Ferrlecit®

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the

upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
	_____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

cc:
Archival NDA 20-955/S-003
HFD-180/B.Strongin
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

/s/

Hugo Gallo Torres
3/27/01 01:20:47 PM
signing for Lilia talarico, M.D., Division Director

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-955

Watson Pharma, Inc.
Attention: Lidia D. Mostovy
Associate Director, Regulatory Liaison
360 Mt. Kemble Avenue
P.O. Box 1953
Morristown, NJ 07962

Dear Ms. Mostovy:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferrlecit® (ferric sodium gluconate complex in sucrose injection).

The Pediatric Research Equity Act ("PREA") was enacted on December 3, 2003. PREA provides that for applications submitted between April 1, 1999, and December 3, 2003, where pediatric studies were not submitted with the application and neither a waiver nor a deferral of pediatric studies was granted under the regulations in effect at the time the application was submitted, the applicant must obtain a waiver or must submit studies by the later of December 3, 2004, or a date specified by the Agency in response to a request for a deferral. Your application, dated August 2, 2000, was submitted without pediatric studies. Further, you were not granted a waiver or a deferral of pediatric studies under the regulations in effect at the time this application was submitted. Under PREA, please submit the required pediatric assessments by December 3, 2004. If you believe your application qualifies for a waiver or deferral of pediatric studies under PREA, submit a letter requesting waiver or deferral and stating the basis for your request within 60 days of the date of this letter.

If you have any questions, call Tanya Clayton, B.S., Regulatory Project Manager, at (301) 827-4005.

Sincerely,

{See appended electronic signature page}

Brian K. Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastrointestinal and Coagulation
Drug Products, HFD-180
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Brian Strongin
6/4/04 12:23:44 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-955/S-003

Watson Laboratories, Inc.
Attention: Dorothy Frank, M.S., R.A.C.
Director, Regulatory Affairs
Research Park
417 Wakara Way
Salt Lake City, UT 84108

Dear Ms. Frank:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferrlecit® (sodium ferric gluconate complex in sucrose injection).

We also refer to your December 30, 1998 submission to NDA 20-955 in response to our November 2, 1998 request for commitment, in writing, to specific phase IV studies. Your response included a request for a full waiver from the requirement for pediatric studies in the neonate (birth to 1 month of age) and infant (1 month to 2 years of age) age groups.

Finally, we refer to your January 4, 1999 submission to NDA 20-955 containing a proposed pediatric study request and to our June 25, 1999 response. Your submission included Protocol FER 9804 entitled, "Open-label, Controlled, Randomized, Multicenter, Comparative Study of the Safety and Efficacy of Two Doses of Ferrlecit® (Sodium Ferric Gluconate Complex in Sucrose Injection) Versus Oral Iron in the Treatment of Iron Deficiency in Childhood Hemodialysis Patients on Epoetin". This study is designed for the child age group (2 to 12 years). It also included Protocol FER 9802 entitled, "Open-Label Study for Single-Dose Pharmacokinetics of Ferrlecit® (Sodium Ferric Gluconate Complex in Sucrose Injection) Following Intravenous Administration to Adolescent Hemodialysis Patients on Epoetin". This study is designed for the adolescent age group (12 years to < 16 years).

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55. In your annual report to IND 47,764 dated June 9, 2000 you stated that a response to our June 25, 1999 letter was being prepared.

Please clarify your plans to evaluate the need for a test dose and administration of Ferrlecit® undiluted as a slow IV injection in the pediatric population as well as your progress toward fulfilling your phase IV commitment in pediatric patients.

If you have any questions, call Brian Strongin, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

{See appended electronic signature page}

Lilia Talarico, M.D.
Director
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lilia Talarico
7/12/01 06:31:04 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-955/S-003

Watson Laboratories, Inc.
Attention: Ms. Dorothy A. Frank
Executive Director, Regulatory Affairs
417 Wakara Way,
Salt Lake City, UT 84108

Dear Ms. Frank:

We acknowledge the receipt of your August 7, 2001 submission containing final printed labeling in response to our February 2, 2001 letter approving your supplemental new drug application for Ferrlecit® (sodium ferric gluconate complex in sucrose injection).

We have reviewed the package insert labeling that you submitted in accordance with our February 2, 2001 letter, and we find it acceptable. However, we request that you make the following revisions at the next printing.

1. Provide both the proprietary and established name at the first mention of the drug name on each of the four pages of the package insert as required under 21 CFR 201(10)(g). Further, in the established name, the "s" in the word "sodium" should be a lower case letter.

2. In the CLINICAL STUDIES section, the "Study A" and "Study B" subsections, provide the following information for patients participating in the studies: proportions of male and female patients, proportions of patients by race and ethnicity, and age range/mean age.

3. After the HOW SUPPLIED section, revise the "**Caution: Rx Only**" statement to read (in bolded type): "**Rx Only**".

4. After the HOW SUPPLIED section, provide the following phrase (in bolded type): "**Keep out of the reach of children**."

If you have any questions, call Karen Oliver, Regulatory Project Manager, at (301) 827-7457.

Sincerely,

Victor F. C. Raczkowski, M.D., M.Sc.
Acting Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Victor Raczkowski
9/26/01 03:01:00 PM

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-955/S-003

Name of Drug: Ferrlecit® (sodium ferric gluconate complex in sucrose injection)

Sponsor: R & D Laboratories, Inc.

Material Reviewed

Submission Date(s): August 7, 2001

Receipt Date(s): August 8, 2001

Background and Summary Description: Supplement 003, submitted August 2, 2000, provides for changes to the following sections of package insert: DESCRIPTION, CLINICAL PHARMACOLOGY, CLINICAL STUDIES, WARNINGS, ADVERSE REACTIONS, OVERDOSAGE, and DOSAGE AND ADMINISTRATION.

The supplement was approved February 2, 2001. The sponsor submitted final printed labeling (FPL) in response to the approval letter.

Review

Package Insert

The FPL for the package insert, identified "502523 June 2001" was compared to the labeling text enclosed in the February 2, 2001 approval letter. The package inserts are identical except for the following:

1. Logo and bar coding has been added.

   These changes are ACCEPTABLE.

2. Minor typographical and punctuation changes were noted.

   These changes are ACCEPTABLE.

3. Although not mentioned in the February 2, 2001 approval letter, this reviewer notes that the proprietary and established names are not used at the first mention of the drug name on each of the four pages of the package insert as required under 21 CFR 201(10)(g). Further, in the established name, the "s" in the word "sodium" should be a lower case letter.

   This is UNACCEPTABLE. The sponsor should be requested to revise the package insert as required under 21 CFR 201.10(g).

4. Although not mentioned in the February 2, 2001 approval letter, this reviewer notes that in the CLINICAL STUDIES section, the "Study A" and "Study B" subsections, information regarding the patients participating in the studies does not include the following: proportions of male and female patients, proportions of patients by race and ethnicity, and age range/mean age.

5. Although not mentioned in the February 2, 2001 approval letter, this reviewer requests that after the HOW SUPPLIED section, the "**Caution: Rx Only**" statement be revised to read "**Rx Only**".

6. Although not mentioned in the February 2, 2001 approval letter, this reviewer requests that after the HOW SUPPLIED section, the following phrase be added in bolded type: "**Keep out of the reach of children.**"

Conclusion

An acknowledge and retain letter should be issued. The sponsor should be requested to implement the labeling changes, as identified in 3., 4., 5., and 6. above, at the next printing.

Karen Oliver, RN, MSN
Regulatory Health Project Manager

Lilia Talarico, M.D.
Division Director

R/D init: K.Robie-Suh 09/20/01
R/D init: L.Talarcio 09/20/01

R/D init: V.Raczkoski 09/24/01

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Karen Oliver
9/25/01 12:00:39 PM
CSO

Victor Raczkowski
9/26/01 02:56:26 PM
MEDICAL OFFICER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: January 25, 2001

To: Jur Strobos, M.D.	**From:** Brian Strongin
Company: R&& D Laboratories, Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (202) 234-0399	**Fax number:** (301) 443-9285
Phone number: (202) 518-6377	**Phone number:** (301) 827-7310

Subject: Questions Regarding Labeling for NDA 20-955/S-003

Total no. of pages including cover: 2

Comments:

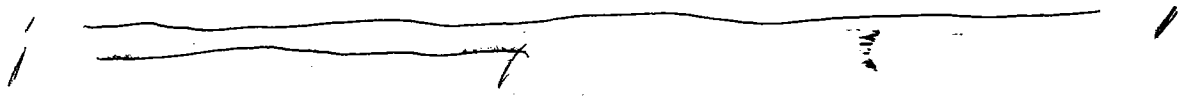
Please see the attached questions

Document to be mailed: ☐ YES ☑ NO

Regarding the proposed labeling for NDA 20-955/S-003:

1. At our meeting last Friday, January 19, 2001, you stated that you had additional data supporting the proposed structure of Ferrlecit®, in particular the role of gluconate in the structure. Please provide these data as soon as possible.

2. On page 6 of the proposed labeling (redline/strikeout) attached to your letter dated January 22, 2001, in the first paragraph of the ADVERSE REACTIONS section it is stated that:



The currently approved labeling stated six patients from "medical reports and North American Clinical trials" and we counted an additional nine patients in Study FER 9803. Please clarify how the number was determined.

3. In several places in the January 22, 2001 proposed labeling it is stated that 126 patients received Ferrlecit® in Studies A and B. We counted patients receiving Ferrlecit® in those studies. Please clarify the discrepancy.

/s/

Brian Strongin
1/25/01 12:06:18 PM
CSO

20 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 20-955 5003

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: January 30, 2001

To: Jur Strobos, M.D.	**From:** Brian Strongin
Company: R & D Laboratories, Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (202) 234-0399	**Fax number:** (301) 443-9285
Phone number: (202) 518-6377	**Phone number:** (301) 827-7310

Subject: Marked-up draft labeling.

Total no. of pages including cover: 2

Comments:

The marked-up draft labeling based on your proposed labeling submitted January 22, 2001 is attached. A few additional comments may be coming Monday, January 29, 2001

Document to be mailed: ☐ YES ☑ NO

Concerning the number of events in Study FER9803 and the proposed labeling:

1. FER9803-drug intolerance events

   Based on information in Volume 5 (page 1), Volume 6 (page 11), and Volume 8 IV.E.1.c (xxxii) 67-028 case report form in the August 2, 2000 submission to S-003, one additional patient (-028) had a drug intolerance event that was not included in the study report as a drug intolerance event. This patient developed itching following Ferrlecit® administration and required permanent cessation of drug therapy per the investigator. Therefore, there were a total of 9 patients who had drug intolerance events in the Study FER9803 interim report.

2. FER9803-suspected allergic events

   The above case (-028) was classified by you as having a suspected allergic event based on information in S-003 Volume 5 (page 1), Volume 6 (page 11), and Volume 8 IV.E.1.c)(xxxii) -028 case report form. Therefore, there were total of 9 patients who had suspected allergic events in Study FER9803.

   According to the definition of "allergic adverse event" in S-003 Volume 5 IV.E.1.a) (i) protocol and the protocol amendments on page 24, pruritus should be considered as a symptom of an allergic reaction.

3. Labeling-Adverse Reactions

   On line 238 of the clean copy of the proposed labeling faxed to you 1/26/01, should be changed to "twelve patients" (9 from Study FER9803 plus 3 from the previous studies) who experienced serious reactions that precluded further therapy with Ferrlecit®.

   Hypersensitivity reactions:

   On line 244 of the labeling, should be changed to "9 patients (0.8%)" who had an adverse event

   These included one life-threatening reaction, 6 allergic reactions and 2 other reactions(Appropriate changes should be made to lines 246 and 247 also.

/s/

Brian Strongin
1/30/01 11:57:54 AM
CSO

Division of Gastrointestinal & Coagulation Drug Products

PROJECT MANAGER'S REVIEW

Application Number: NDA 20-955/SE8-003

Name of Drug: Ferrlecit® (sodium ferric gluconate complex in sucrose injection)

Sponsor: R&D Laboratories, Inc.

Material Reviewed

Submission Date: August 2, 2000

Receipt Date: August 2, 2000

Background and Summary Description: NDA 20-955/SE8-003 provides for changes to the following sections of the approved labeling: DESCRIPTION, CLINICAL PHARMACOLOGY, CLINICAL STUDIES, WARNINGS, ADVERSE REACTIONS, OVERDOSAGE, and DOSAGE AND ADMINISTRATION. Interim data from the Phase IV Study FER 9803 as well as data from the Phase IV Study FER 9801 and other data and information support these changes. The sponsor's proposed labeling will be compared to the currently approved labeling and the differences noted below.

Review

The sponsor's proposed labeling differs from the currently approved labeling in the following ways:

1. All references to erythropoietin were standardized to epoetin.

2. The phrase "iron saturation" was changed to "transferrin saturation" wherever it occurred.

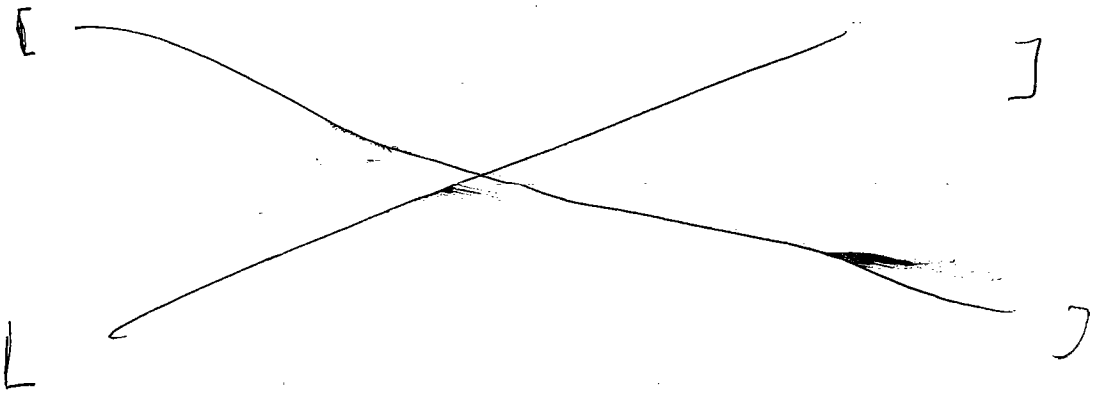
3. The underlined text in the first four paragraphs of the CLINICAL PHARMACOLOGY section below was added. Please note that this text was <u>not</u> underlined in the sponsor's underline/strikeout version of the proposed labeling.

   CLINICAL PHARMACOLOGY

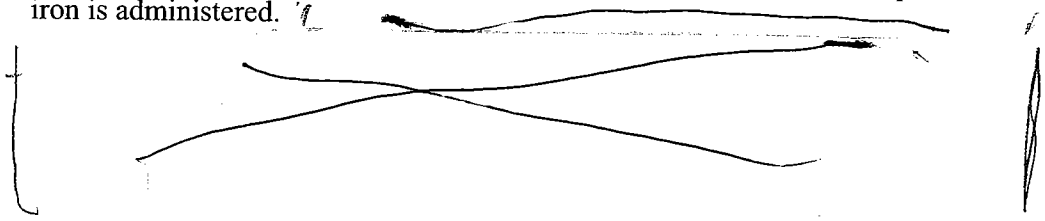
   Ferrlecit® is used to replete the total body content of iron. Iron is critical for normal hemoglobin synthesis to maintain oxygen transport. Additionally, iron is necessary for metabolism and synthesis of DNA and various enzymatic processes.

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 (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 can include increased iron utilization (e.g., from epoetin 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 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 epoetin dosage with stable hemoglobin/hematocrit when parenteral iron is administered.



4. The underline and strikeout text in the sponsor's proposed labeling included in the August 2, 2000 submission were added to and deleted from the currently approved labeling.

Conclusions

Marked-up draft labeling based on the sponsor's proposed labeling will be prepared when all reviews have been completed. A labeling meeting with the sponsor is scheduled for January 19, 2001.

Regulatory Health Project Manager

cc:
NDA 20-955/SE8-003
HFD-180/B.Strongin
HFD-180/L.Talarico
HFD-180/K.Robie-Suh
HFD-180/M.Lu
HFD-870/S.Doddapaneni
HFD-870/S.Al-Fayoumi
HFD-180/L.Zhou
HFD-180/R.Frankewich
HFD-870/T.Permutt
HFD-870/W.J.Chen

Drafted by: BKS/December 22, 2000
Final: BKS/December 21, 2000
Filename: 20955012.0

PM REVIEW

/s/

Brian Strongin
12/22/00 02:39:44 PM
CSO

Mark Avigan
12/22/00 02:50:57 PM
MEDICAL OFFICER
Acting Director, Division of Gastrointestinal and Coagulation Drug Products [12/22/00]

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: 11/20/00

To: Jur Strobos, M.D.	**From:** Brian Strongin
Company: R & D Laboratories, Inc.	Division of GI and Coagulation Drug Products
Fax number: (202) 234-0399	**Fax number:** (301) 443-9285
Phone number:	**Phone number:**

Subject: Statistical information request

Total no. of pages including cover: 2

Comments:

Please see the attached information request.

Document to be mailed: ☐ YES xNO

Please provide the following information for NDA 20-955/S-003 regarding the suspected allergic events discussed on page 58 of Volume 38.5and the all adverse events discussed on page 79 of Volume 38.5 for Study FER9803:

In the 2 by 2 cross-over design, each subject supplies a pair of observations (0, 0), (0, 1), (1, 0), and (1, 1) where (a, b) indicates response a in period 1 and b in period 2. We can therefore, summarize the data from one 2 by 2 trial in the form a 2 * 4 contingency table:

	(0, 0)	(0, 1)	(1, 0)	(1, 1)	ROW TOTAL
1. (F, P)	N_{11}	N_{12}	N_{13}	N_{14}	$N_{1.}$
2. (P, F)	N_{21}	N_{22}	N_{23}	N_{24}	$N_{2.}$
Column Total	$N_{.1}$	$N_{.2}$	$N_{.3}$	$N_{.4}$	$N_{..}$

In the table, the entry N_{11} for example is the number of subjects in sequence group 1 (subjects receiving Ferrlecit® in the first period and Placebo in the second period) who gave a (0, 0) response. The other entries in the body of the table are defined in a similar way and the sizes of the two groups are given by the marginal totals $N_{1.}$ and $N_{2.}$.

For the suspected allergic events, 0 stands for a subject without a suspected allergic event and 1 stands for a subject with a suspected allergic event. For the all adverse events, 0 is for a subject without an all adverse event and 1 is for a subject with an all adverse event.

Please fill out the number of subjects (N) in the above table separately for suspected allergic events and all adverse events. Based on the above table, please perform McNemar and Fisher exact tests for both suspected allergic events and all adverse events.

/s/

Brian Strongin
11/20/00 04:14:31 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: 11/17/00

To: Jur Strobos, M.D.	**From:** Brian Strongin
Company: R & D Laboratories, Inc.	Division of Gastrointestinal and Coagulation Drug Products
Fax number: (202) 234-0399	**Fax number:** (301) 443-9285
Phone number:	**Phone number:**

Subject: NDA 20-955/S-003 clinical information request.

Total no. of pages including cover: 2

Comments:

Please see the attached clinical information request.

Document to be mailed: ☐ YES x NO

Please clarify the following discrepancies regarding the number of life-threatening events in the iron dextran publications described in the FER 9803 Protocol and in the Interim Analysis Study Report for Study FER 9803 (Volume 38.5):

1. **4 iron dextran publications are listed in the protocol while 3 publications are listed in the Study Report;**
2. **18 events are listed in three publications in the protocol while 20 events are listed in three publications in the Study Report.**

/s/

Brian Strongin
11/17/00 09:13:17 AM
CSO

Division of Gastrointestinal & Coagulation Drug Products

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: NDA 20-955/SE8-003

Name of Drug: Ferrlecit® (ferric sodium gluconate complex in sucrose injection)

Sponsor: R&D Laboratories, Inc.

Material Reviewed

Type of Submission (i.e., paper, electronic, or combination): Paper

Submission Date: August 2, 2000

Receipt Date: August 2, 2000

Filing Date: October 1, 2000

User-fee Goal Date: February 2, 2001

Proposed Indication: iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental epoetin

Other Background Information:

NDA 20-955 was approved February 18, 1999. The sponsor agreed to several Phase IV commitments including to: (1) provide additional safety data (e.g., the incidence of allergic or anaphylactic reactions or cross-reactivity with other intravenous iron preparations); (2) conduct a study to evaluate the possibly increased risk of allergic/anaphylactic reactions in patients receiving angiotensin converting enzyme inhibitors and Ferrlecit® concurrently; and (3) conduct a pilot human pharmacokinetic study of Ferrlecit®. In order to fulfill these commitments, the sponsor is conducting: (1) Study FER 9803 entitled, "Crossover, Randomized, Blinded, Prospective, Multicenter Clinical Evaluation of the Rate of Adverse Effects to Ferrlecit® in Hemodialysis Patients as Compared to Placebo"; (2) Study FER 9806 entitled, "Open-Label, Prospective, Multicenter Study to Evaluate the Rate of Adverse Events and Their Relationship to Concomitant Administration of Angiotensin Converting Enzyme Inhibitor Therapy following Repeated Administration of Ferrlecit® (ferric sodium gluconate complex in sucrose injection) in Hemodialysis Patients Receiving Erythropoietin"; and (3) Study FER 9801 entitled, "Open-Label, Dose Ranging Study to Determine the Single-Dose Pharmacokinetics of Ferrlecit® (sodium ferric gluconate complex in sucrose injection) Following Intravenous Administration to Healthy, Iron Deficient Volunteers".

On February 29, 2000, the sponsor and the Division met to discuss a proposed supplement

providing for labeling changes to the Description, Clinical Pharmacology, Clinical Studies, Warnings, Adverse Events, Overdosage, and Dosage and Administration sections of the package insert. These changes were to be supported by interim data from Study FER 9803 as well as other data and information. SE8-003 was submitted August 2, 2000 and provides for most of the changes discussed at this meeting.

Review

PART I: OVERALL FORMATTING[a,d,e]

[Note: Items 1,2,3,4, & 5 must be submitted in paper with original signature.]	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Cover Letter		X	
2. Form FDA 356h	X		Volume 38.1; Section 1, Page 1
a. Establishment information		X	N/A
b. Reference to DMF(s) & Other Applications		X	N/A
3. User Fee FDA Form 3397	X		Original: Volume 38.9, Section V Revised: Submitted August 3. Reflects user fee payment.
4. Patent information & certification		X	N/A
5. Debarment certification (Note: Must have a definitive statement)		X	Requested from sponsor 9/5/00
6. Field Copy Certification		X	Asked firm to submit a field copy 9/5/00

7. Financial Disclosure		X	Requested from sponsor 9/5/00
8. Comprehensive Index	X		Volume 38.1, Section II, Pages 1-8
9. Pagination	X		Each section paginated separately. Acceptable.
10. Summary Volume		X	Summary section. Volume 1; Section III
11. Review Volumes	X		Clinical, Stat, CMC, Pharm/tox, and Biopharm,
12. Labeling (PI, container, & carton labels)	X		
a. unannotated PI	X		Volume 1; Section III.A.1.b.
b. annotated PI	X		Volume 1; Section III.A.1.a.
c. immediate container		X	N/A
d. carton		X	N/A
e. patient package insert (PPI)		X	N/A

f. foreign labeling (English translation)		X	N/A
13.Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	X		Study FER 9801: Volume 38.3; Section IV.C.1.a.16.3 and Volume 38.4; Section IV.C.1.a.16.4.3g Study FER 9803: Volume 38.5; Section IV.E.1.a.iii
14.Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	X		Study FER 9803: Volume 38.6; Section IV.E.1.c.

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY[b,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	X		Volume 38.1; Section III.B.
2. Foreign Marketing History	X		Volume 38.1; Section III.C.
3. Summary of Each Technical Section			
a. Chemistry, Manufacturing, & Controls (CMC)		X	Corresponding technical section is very short. Summary is unnecessary.

b. Nonclinical Pharmacology/Toxicology		X	Corresponding technical section is very short. Summary is unnecessary.
c. Human Pharmacokinetic & Bioavailability		X	Will request from the sponsor if reviewer and team leader feel it is necessary.
d. Microbiology		X	N/A
e. Clinical Data & Results of Statistical Analysis		X	Reviewing Medical Officer feels this section is unnecessary.
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies		X	N/A
5. Summary of Safety		X	The Medical Officer has requested a summary and analysis of available safety data, other than that from FER 9803, since approval. Data from adverse event reports and from the literature should be included. This was requested from the sponsor on 9/5/00.
6. Summary of Efficacy		X	N/A

Y=Yes (Present). N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS[c,d,e]

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. List of Investigators		X	Study FER 9803: The Medical Officer has requested a list of investigators or the location in the supplement of this list. Requested from the sponsor 9/5/00.
2. Controlled Clinical Studies			
a. Table of all studies		X	FER 9803 is the only controlled, clinical study.
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	X		Synopsis: Volume 38.5; Section IV.E.1.a.; page 8 Protocol: Volume 38.5; Section IV.E.1.a.i Related Publications: Volumes 38.9-38.10; Section IV.E.1.a.(ix) – (xi) List of Investigators: List or location of list has been requested from the sponsor. Clin/Stat Report: Volume 38.5;Section IV.E.1.a.
c. Optional overall summary & evaluation of data from controlled clinical studies		X	N/A
3. Integrated Summary of Efficacy (ISE)		X	N/A
4. Integrated Summary of Safety (ISS)		X	The Medical Officer has requested a summary and analysis of available safety data, other than that from FER 9803, since approval. Data from adverse event reports and from the literature should be included. This was requested from the sponsor on 9/5/00.
5. Drug Abuse & Overdosage Information		X	N/A

6. Integrated Summary of Benefits & Risks of the Drug		X	N/A
7. Gender/Race/Age Safety & Efficacy Analysis Studies		X	Per the Medical Officer, this will be requested from the sponsor.

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS[d,e]

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population		X	N/A
2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.)		X	SAS datasets will be requested for Study FER9803 per the Medical Officer.
a. Proposed unannotated labeling in MS WORD		X	Will be requested from the sponsor.
b. Stability data in SAS data set format (only if paper submission)		X	N/A
c. Efficacy data in SAS data set format (only if paper submission)		X	N/A
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)		X	We will discuss the need for this at the filing meeting.
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)		X	N/A
3. Exclusivity Statement		X	N/A

Y=Yes (Present), N=No (Absent)

[a]"GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[b]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

[c]"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

[d]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-GENERAL CONSIDERATIONS" (JANUARY 1999).

[e]"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-NDAS" (JANUARY 1999).

Conclusions

From an administrative standpoint, this application is filable.

The following information was requested from the firm September 5, 2000:

1. a debarment certification;
2. a copy of the application submitted to the appropriate field office;
3. a financial disclosure statement;
4. a summary and analysis of the available safety data (other than that from Study FER9803) since approval, including adverse event reports and literature data;
5. a list of investigators for Study FER9803;
6. gender, race, and age analyses of Study FER9803;
7. SAS datasets for Study FER9803;
8. and, the proposed unannotated labeling in MS WORD 97.

A planning/filing meeting is scheduled for September 20, 2000.

_____

Name
Regulatory Project Manager

cc:
Original NDA
HFD-180/Div. Files
HFD-180/RPM/
HFD-180/Talarico
HFD-180/Reviewers
draft: BKS/September 5, 2000
r/d Initials: LT/September 5, 2000
final: BKS/September 5, 2000
ADMINISTRATIVE REVIEW

NDA 20-955/S-003

PRIOR APPROVAL SUPPLEMENT

R&D Laboratories, Inc.
Attention: Jur Strobos, M.D., J.D.
Vice President, Clinical and Regulatory Affairs
4640 Admiralty Way, Suite 710
Marina del Rey, CA 90292

Dear Dr. Strobos:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Ferrlecit® (ferric sodium gluconate complex in sucrose injection)

NDA Number: 20-955

Supplement Number: S-003

Review Priority Classification: Priority (P)

Date of Supplement: August 2, 2000

Date of Receipt: August 2, 2000

This supplement proposes changes to the following sections of the approved package insert: DESCRIPTION, CLINICAL PHARMACOLOGY, CLINICAL STUDIES, WARNINGS, ADVERSE REACTIONS, OVERDOSAGE and DOSAGE AND ADMINISTRATION.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 1, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 2, 2001.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7310.

Sincerely,

Brian Strongin
Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 20-955
HFD-180/Div. Files
HFD-180/B.Strongin
HFD-180/M.Lu
DISTRICT OFFICE

Drafted by: BKS/August 28, 2000
final: BKS/August 28, 2000
filename: 20955008.0

PRIOR APPROVAL SUPPLEMENT ACKNOWLEDGMENT (AC)