CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-955/S-001

Trade Name: Ferrlecit Injection

Generic Name: Sodium Ferric Gluconate Complex in Sucrose

Sponsor: Watson Laboratories, Inc.

Approval Date: July 29, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-955/S-001

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-955/S-001

APPROVAL LETTER

NDA 20-955/S-001

R & D Laboratories, Inc.
Attention: Jur Strobos, M.D.
4640 Admiralty Way, Suite 710
Marina del Rey, CA 90292

Dear Dr. Strobos:

Please refer to your supplemental new drug application dated March 15, 1999, received March 16, 1999, 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 submission dated July 16, 1999. Your submission of July 16, 1999 constituted a complete response to our July 15, 1999 action letter.

This supplemental new drug application provides for INSERT THE CHANGES.

We have completed the review of this supplemental application and it is approved.

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, contact Brian Strongin, Project Manager, at (301) 827-7310.

Sincerely,

Eric P. Duffy, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug Products, (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 20-955
HFD-180/Div. Files
HFD-180/B.Strongin
HFD-180/E.Duffy
HFD-180/R.Frankewich

HFD-95/DDMS (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: BKS/July 27, 1999
Initialed by:
final:
filename:

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-955/S-001

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-001

CHEMISTRY REVIEW(S)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls Supplement

NDA#:20-955SUPPLEMENT#:SCE-001 CHEM REVIEW#:2 REVIEW DATE:7/23/99

SUBMISSION TYPE	DATES				
	DOCUMENT ST	CDER	ASSIGNED	REVIEW	NUM LETTER
ORIGINAL	3/16/99	3/16/99	3/19/99	7/2/99	
AMENDMENT	4/7/99	4/8/99	-	-	
AMENDMENT	7/16/99	7/19/99	7/21/99	7/23/99	

SUPPLEMENT PROVIDES FOR:
Extension of the expiration date of the drug product to eighteen (18) months.

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)

SUPPORTING DOCUMENTS:

DMF Number	Item referenced	Holder	Status	Review Date	Letter Date
None					

RELATED DOCUMENTS (if applicable): N/A

CONSULTS:
None

REMARKS/COMMENTS:
The original application proposed a 18-month expiration date, based on the real-time, room-temperature data available (which was 18 months). The amendment submitted on April 7, 1999 provides statistical calculations (using the SAS program) on the existing stability data (

That data show that (real-time room temperture data at 18 months) a ferrous iron content which is of its specification had been acheived. There appears to be a marked increase in the level of ferrous iron in all three lots up to 12 months. From 12 to 18 months, this level appears to have stablized.

A review of the statistical calcualtions by HFD-715 showed that the predicted expiration date is about

The firm was informed of this conclusion in a letter from this division dated July 15, 1999. This amendment was filed by the firm in order to reinstate its request for an extension of the expiration date from 12 to 18 months, based on real-time data.

CONCLUSIONS & RECOMMENDATIONS:
The extension of the expiration date for the drug product from 12 to 18 months date is acceptable. This supplement (as amended in the July 16, 1999 letter from the firm) may be approved.

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

Eric P. Duffy, Ph.D.
Chemistry Team Leader, HFD-180

cc:
NDA #20-955
HFD-180/LTalarico
HFD-180/Div File/NDA #20-955
HFD-180/EDuffy
HFD-180/RFrankewich
HFD-181/BStrongin
R/D Init by:

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls Supplement

NDA#:20-955 SUPPLEMENT#:SCE-001 CHEM REVIEW#:1 REVIEW DATE:7/2/99

SUBMISSION TYPE	DATES					
	DOCUMENT	CDER	ASSIGNED	REVIEW	NUM LETTER	ST
ORIGINAL	3/16/99	3/16/99	3/19/99	7/2/99		
AMENDMENT	4/7/99	4/8/99	-	-		

SUPPLEMENT PROVIDES FOR:
Extension of the expiration date of the drug product

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)

SUPPORTING DOCUMENTS:

DMF Number	Item referenced	Holder	Status	Review Date	Letter Date
None					

RELATED DOCUMENTS (if applicable): N/A

CONSULTS:
This supplement was reviewed by Ferrin Harrison, Ph.D. in HFD-715 in order to evaluate whether or not the submitted data is appropriate to support the [redacted]

REMARKS/COMMENTS:
The original application proposed a 18-month expiration date, based on the real-time, room-temperature data available (which was 18 months). The amendment submitted on April 7, 1999 provides statistical calculations (using the SAS program) on the existing stability data [redacted].

That data show that (real-time room temperture data at 18 months) a ferrous iron content which is [redacted] of its specification had been acheived. There appears to be a marked increase in the level of ferrous iron in all three lots up to 12 months. From 12 to 18 months, this level appears to have stablized.

A review of the statistical calcualtions by HFD-715 showed that the predicted expiration date is about [redacted]

Until data is generated that shows the stabilizing trend to be longer lasting than just one stability timepoint, the expiration date for this product should not be extended beyond what the real-time stability data will allow.

CONCLUSIONS & RECOMMENDATIONS:
The extension of the expiration date is acceptable, so the supplement may be approved; however, it is recommended that the expiration date be extended to 18 months [redacted]

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

Eric P. Duffy, Ph.D.
Chemistry Team Leader, HFD-180

cc:
NDA #20-955
HFD-180/LTalarico
HFD-180/Div File/NDA #20-955
HFD-180/EDuffy
HFD-180/RFrankewich
HFD-181/BStrongin
R/D Init by:

4 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 26-955
S001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-955/ S-001

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

NDA 20-955/S-001

R & D Laboratories, Inc.
Attention: Jur Strobos, M.D.
4640 Admiralty Way, Suite 710
Marina del Rey, CA 90292

Dear Dr. Strobos:

Please refer to your supplemental new drug application dated March 15, 1999, received March 16, 1999, 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 our approval letter for this supplemental new drug application dated July 29, 1999. In that letter, we mistakenly stated that this application proposes an extension of the expiry / ——— /. In your submission of July 16, 1999 you requested approval of an expiry of 18 months. Our statement should have read that this supplemental application, "...proposes an extension of the expiry to 18 months." Please be aware that S-001 was approved for an extension of the expiry to 18 months only, / ——— /

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

Sincerely,

Eric P. Duffy, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug Products, (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 20-955
HFD-180/Div. Files
HFD-180/B.Strongin
HFD-180/E.Duffy
HFD-180/R.Frankewich
HFD-95/DDMS (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: BKS/July 29, 1999
Initialed by: EPD/July 29, 1999
final: BKS/July 29, 1999
filename: 20955907.2

APPROVAL (AP)

NDA 20-955/S-001

R & D Laboratories, Inc.
Attention: Jur Strobos, MD
4640 Admiralty Way, Suite 710
Marina del Rey, California 90292

Dear Dr. Strobos:

We acknowledge receipt of your manufacturing supplemental application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

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

NDA Number: 20-955

Supplement Number: S-001

Date of Supplement: March 15, 1999

Date of Receipt: March 16, 1999

This supplement proposes an extension of the expiry to 18 months.

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 May 15, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be July 16, 1999 and the secondary user fee goal date will be September 16, 1999.

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, contact 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/R.Frankewich
DISTRICT OFFICE

Drafted by: BKS/April 5, 1999
final: BKS/April 5, 1999
filename: 20955904.0

SUPPLEMENT ACKNOWLEDGEMENT (AC)

NDA 20-955/S-001

R & D Laboratories, Inc.
Attention: Jur Strobos, M.D.
4640 Admiralty Way, Suite 710
Marina del Rey, California 90292

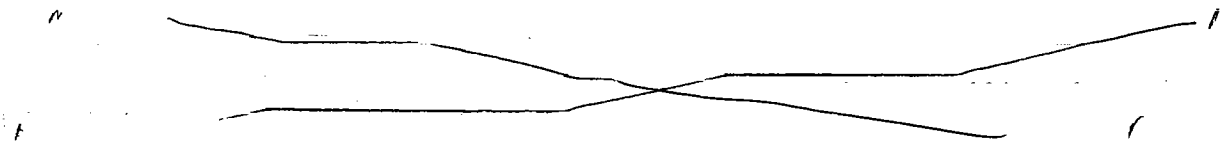
Dear Dr. Strobos:

Please refer to your supplemental new drug application dated March 15, 1999, received March 16, 1999, 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 submission dated April 7, 1999 that includes the results of a SAS statistical analysis on the 18-month real time stability data submitted in this supplemental application.

This supplement [redacted]

We have completed our review and find the information presented is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiency may be summarized as follows:



Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change prior to approval of this supplemental application.

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

Sincerely,

Eric P. Duffy, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug Products,
(HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 20-955
HFD-180/Div. Files
HFD-180/B.Strongin
HFD-180/E.Duffy
HFD-180/R.Frankewich
HFD-95/DDMS
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: BKS/July 15, 1999
Initialed by: EPD/July 15, 1999
final: BKS/July 15, 1999
filename: 20955907.0

NOT APPROVABLE (NA)