Clinical Review
NDA 20-955/SE5-006

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Sponsor:	Watson Pharma, Inc.
Drug name:	Ferrlecit (Iron Gluconate Complex in Sucrose Injection)
Drug class:	Intravenous iron product
Indication:	Treatment of iron deficiency anemia in pediatric patients undergoing chronic hemodialysis who are receiving supplemental epoetin therapy
Date submitted:	February 13, 2004
Review completed:	July 7, 2004
Medical Reviewer:	Min Lu, M.D., M.P.H.

Table of Contents

LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
AUC_{0-t}	area under the Ferrlecit concentration vs. time curve from time 0 to time t
$AUC_{0-\infty}$	area under the Ferrlecit concentration vs. time curve from time 0 to infinity
BUN	blood urea nitrogen
CHr	reticulocyte hemoglobin content
Cl	Ferrlecit clearance
Cmax	maximum measured serum Ferrlecit concentration
COSTART	Coding System for a Thesaurus of Adverse Reaction Terms
CRF	case report form
CV	coefficient of variation
EPO	erythropoietin
ESRD	end stage renal disease
HCRBC	% hypochromic red blood cell
Hct	hematocrit
HD	hemodialysis
HEENT	head, ears, eyes, nose, throat
Hgb	hemoglobin
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
K_{el}	apparent Ferrlecit elimination rate constant
Kt/V	dialysis adequacy
LDH	lactate dehydrogenase
LTF	lost to follow-up
NAPRTCS	North American Pediatric Renal Transplant Case Studies
NDA	new drug application
NKF-K/DOQI	National Kidney Foundation's Kidney Disease Outcomes Quality Initiative
NONMEM	non-linear mixed effect model
OC	observed cases
PK	pharmacokinetics
RBC	red blood cell
RES	reticulo-endothelial system
RSV	rescreening visit
SAE	serious adverse event
SD	standard deviation
SEM	standard error of the mean
SV	screening visit
T1/2	Ferrlecit terminal half-life
T max	time required from the beginning of the Ferrlecit infusion to reach
TSAT	% transferrin saturation
U	International Unit
URR	urea reduction ratio
US	United States
Vd	Ferrlecit volume of distribution
WBC	white blood cell

Clinical Review for NDA 20-955/SE5-006

Executive Summary

I. Recommendations

A. Recommendation on Approvability

From a clinical perspective, Ferrlecit is approvable for the treatment of iron deficiency anemia in pediatric patients 6 to 15 years of age who are undergoing chronic hemodialysis and who are receiving supplemental epoetin therapy. The recommended dose regimen is 0.12 mL/kg (1.5 mg/kg of elemental iron) by intravenous infusion during eight consecutive hemodialysis sessions.

One multicenter, randomized, double-blind, dose response study was conducted in 67 pediatric patients 6 to 15 years of age undergoing chronic hemodialysis who were receiving epoetin supplemental therapy. The study showed a significant increase in hemoglobin from baseline with Ferrlecit 1.5 mg/kg dosing (0.8 g/dL) and with Ferrlecit 3.0 mg/kg dosing regimen (0.9 g/dL) at 2 weeks after treatment. The safety results showed that more patients in the 3.0 mg/kg dosing group experienced hypotension, tachycardia, fever, headache, abdominal pain, nausea, pharyngitis, and rhinitis than patients in the 1.5 mg/kg dosing group. Based on the benefit/risk analysis, a Ferrlecit dose of 1.5 mg/kg should be recommended for the pediatric patients 6 to 15 years of age.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

No new recommendations on Phase 4 study. Risk management includes that the sponsor should revise labeling as recommended (See appendix).

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Product name: Ferrlecit

Drug class: Intravenous iron products

In response to the Written Request, one pediatric study (FR01006) was conducted in 67 patients with iron deficiency anemia who were undergoing chronic hemodialysis and who were receiving supplemental epoetin therapy to support the indication for treatment of iron deficiency anemia in pediatric patients 6-15 years of age who were undergoing chronic hemodialysis and were receiving supplemental epoetin therapy. The proposed Ferrlecit dose regimen for pediatric patients 6 to 15 years of age is 0.12 mL/kg (1.5 mg/kg of elemental iron) by intravenous infusion at eight sequential dialysis sessions.

B. Efficacy

One pediatric study (FR01006) was submitted to support the indication of treatment of iron deficiency anemia in pediatric patients 6-15 years of age undergoing chronic hemodialysis who are receiving supplemental epoetin therapy.

Study FR01006 was a multicenter, randomized, double-blind, parallel groups, dose-response study of Ferrlecit in pediatric patients who underwent chronic hemodialysis and who were receiving supplemental epoetin therapy. Two doses of Ferrlecit (1.5 mg/kg and 3.0 mg/kg of elemental iron) IV infusion were studied and were administered during eight consecutive hemodialysis sessions over an approximately 22 day period. Patients 2 to 15 years of age were eligible for the study. Patients with TSAT<20% and/or serum ferritin <100 ng/mL at baseline and receiving a stable EPO dosing regimen were enrolled in the study. The mean hemoglobin at baseline was 9.4 g/dL in study patients. The primary efficacy endpoint was the change in hemoglobin from baseline to two weeks following the last Ferrlecit administration.

A total of 88 patients were screened, 67 were enrolled and randomized at 21 sites from 5 countries. A total of 66 patients received study drug (32 in the 1.5 mg/kg group and 34 in the 3.0 mg/kg group) and 57 (85%) patients (25 in the 1.5 mg/kg group and 32 in the 3.0 mg/kg group) were evaluated for primary efficacy endpoint. Among the 66 patients who were treated in the study, patients ranged in age from 6 to 15 years (mean age of 12 years) and no children were under 6 years of age due to scarcity of patients in this age range. There were 38 (58%) patients with age 6-12 years and 28 (42%) patients with age 12-15 years. There were similar numbers of male (34, 52%) and female (32, 48%) patients. Majority of patients were Caucasian (Caucasian 71%, Asian 18%, Hispanic 6%, Black 2% and others 3%).

The primary efficacy results showed that the mean increase from baseline in hemoglobin at 2 weeks after the last Ferrlecit administration was 0.8 g/dL in the 1.5 mg/kg group and 0.9g/dL in the 3.0 mg/kg group based on completer patient population (57 patients). The hemoglobin values at 2 weeks after the last Ferrlecit administration were significantly increased in both 1.5 mg/kg and 3.0 mg/kg dosing groups as compared to baseline ($p=0.0033$ and <0.0001, respectively). The mean increase in hemoglobin was maintained at 4 weeks after the treatment in both dosing groups (0.9 g/dL in the 1.5 mg/kg group and 1.0g/dL in the 3.0 mg/kg group). There was no significant difference in mean changes from baseline in hemoglobin at 2 weeks after treatment between the two dosing groups ($p=0.75$). There were similar results based on all treated patient population (66 patients).

Results of the secondary efficacy analyses were consistent with those of the primary efficacy analysis. The response rates (increase in hemoglobin ≥1 g/dL) at 2 weeks after treatment were similar between the two dosing groups (40% in the 1.5 mg/kg group and 50% in the 3.0 mg/kg group, p=0.45). Hematocrit increased 2.6% at 2 weeks after treatment from baseline in the 1.5 mg/kg group [p=0.0031] and 3.0% in the 3.0 mg/kg group [p<0.0001]. There were significant increases from baseline in TSAT (5.5% in the 1.5 mg/kg group [p<0.01] and 10.5% in the 3.0 mg/kg group [p<0.0001]), serum ferritin (192 ng/mL in the 1.5 mg/kg group [p<0.0001]and 314 ng/mL in the 3.0 mg/kg group [p<0.0001]) and CHr (1.3 pg in the 1.5 mg/kg group [p<0.01] and 1.2 pg in the 3.0 mg/kg group [p<0.05]) at 2 weeks after treatment in both dosing groups. HCRBC was not changed at 2 weeks after treatment from baseline in either dosing group. There was no statistically significant difference for any secondary endpoint between the two dosing groups (p>0.05). The results for the secondary efficacy endpoints based on all treated population were similar to those for the completer patient population.

In conclusion, Study FR01006 showed significant increases in hemoglobin at 2 weeks after treatment from baseline in both dosing groups and the effect was maintained at 4 weeks after treatment. There was no significant difference in efficacy between the 1.5 mg/kg and 3.0 mg/kg Ferrlecit dosing regimens.

C. Safety

One study (Study FR01006) was conducted in pediatric patients with iron deficiency anemia who were undergoing chronic hemodialysis and who were receiving supplemental epoetin therapy. A total of 67 patients 6 to 15 years of age were enrolled and 66 patients were treated in the study. Among the 66 patients, 60 (91%) patients received all eight infusions (28 in the 1.5 mg/kg group and 32 in the 3.0 mg/kg group), 3 (4.5%) patients received 7 infusions (2 in the 1.5 mg/kg group and 1 in the 3.0 mg/kg group), and 1 (1.5%) patient each received 5 (in the 3.0 mg/kg group) , 2 (in the 1.5 mg/kg group), and 1 (in the 1.5 mg/kg group) infusion, respectively.

In the study, 81.8% (54/66) of patients reported adverse events. The number of patients reporting adverse events (AEs) was similar between the 1.5 mg/kg treatment group (26 patients, 81.3%, 110 AEs) and the 3.0 mg/ kg treatment group (28 patients, 82.4%, 151 AEs). The overall most common AEs occurring in ≥5%, regardless of treatment group, were: hypotension (35%), headache (24%), hypertension (23%), tachycardia (17%), vomiting (11%), fever (9%), nausea (9%), abdominal pain (9%), pharyngitis (9%), diarrhea (8%), infection (8%), rhinitis (6%), and thrombosis (6%). The study showed that more patients in the higher dosing (3.0 mg/kg) group than in the lower dose group (1.5 mg/kg) experienced the following adverse events: hypotension (41% vs. 28%), tachycardia (21% vs. 13%), fever (15% vs. 3%), headache (29% vs. 19%), abdominal pain (15% vs. 3%), nausea (12% vs. 6%), vomiting (12% vs. 9%), pharyngitis (12% vs. 6%), and rhinitis (9% vs. 3%). Only 4 reported adverse events were considered to be related to study treatment by the investigator (nausea, vomiting, and diarrhea in one patient in the 1.5 mg/kg group, and anemia in one patient in the 3.0 mg/kg group).

There were 52 reported instances of hypotension occurring in 23 patients (34.8%); 14 events occurred in 9 patients (28.1%) in the 1.5 mg/kg treatment group and 38 events occurred in 14 patients (41.2%) in the 3.0 mg/kg treatment group. These instances of hypotension were not considered significant by the investigators for this patient population and were considered by the investigators to be related to the ultrafiltration procedure itself and not to Ferrlecit administration.

No deaths occurred during the study. A total of 12 serious adverse events (SAEs) were reported in 10 patients and the frequency of the reported SAEs was similar between the two dosing groups (5 patients reported 6 SAEs in each dosing groups). The SAEs included hemodialysis catheter related (infection [1], thrombosis [3] and leaking [1]), worsening of hypertension (2), infection (1), overhydration (1), worsening of anemia (1), progression of ESRD (1), and epilepsy (1). Only worsening of anemia was considered by the investigator to be related to the study treatment.

One patient in the 1.5 mg/kg group discontinued treatment due to progression of renal failure requiring kidney transplant. No patients were discontinued due to an adverse event related to study drug treatment in the study. No allergic reaction or anaphylactic reaction to Ferrlecit administration was reported in study.

In conclusion, Study FR01006 showed the frequency of adverse events (about 80%) and serious adverse events (about 15%) was similar between the two dosing groups. The most common adverse events were hypotension (35%), headache (24%), hypertension (23%), tachycardia (17%), vomiting (11%), fever (9%), nausea (9%), abdominal pain (9%), pharyngitis (9%), diarrhea (8%), infection (8%), rhinitis (6%), and thrombosis (6%). More patients in the higher dosing (3.0 mg/kg) group experienced hypotension, tachycardia, fever, headache, abdominal pain, nausea, pharyngitis, and rhinitis than patients in the lower dosing (1.5 mg/kg) group. These safety results were based on pediatric patients 6 to 15 years of age. No safety data were available in pediatric patients younger than 6 years of age.

D. Dosing

Two doses of Ferrlecit (1.5 mg/kg and 3.0 mg/kg) were studied in the trial. Both Ferrlecit dosing regimens showed significant increases from baseline in hemoglobin at 2 weeks after treatment (0.8 g/dL and 0.9 g/dL, respectively). No significant dose-response was seen for change in hemoglobin. The secondary efficacy analysis showed a statistically significant difference in the increase in serum ferritin from baseline to two weeks after the treatment between the two dosing groups (192 ng/mL in the 1.5 mg/kg group and 314 ng/mL in the 3.0 mg/kg group, p=0.0003). This suggests a dose-response relationship between the Ferrlecit dose and the increase in serum ferritin level. No dose-response relationship was observed for other secondary efficacy endpoints including Hct, CHr and HCRBC.

The safety results showed that more patients in the higher dosing (3.0 mg/kg) group experienced hypotension, tachycardia, fever, headache, abdominal pain, nausea, pharyngitis, and rhinitis than those in the lower dosing (1.5 mg/kg) group. This suggests these adverse events are dose-related.

To minimize the risk of adverse reactions with Ferrlecit, the 1.5 mg/kg dosing regimen should be recommended for pediatric patients 6 to 15 years of age in the labeling.

No patients younger than 6 years of age were included in the trial. Therefore, no dose recommendation can be made for patients younger than 6 years of age.

E. Special Populations

Gender

There were 34 males and 32 females who received Ferrlecit infusion in Study FR01006. No significant gender effect was observed in the trial.

Age

There were 38 patients with age of 6 to12 years and 28 patients with age of 13 to 15 years in the study. No patient younger than 6 years of age was enrolled. No significant age effect was observed in the trial.

Race

There were 47 Caucasian, 12 Hispanic, 4 Black, 1 Asians, and 2 others enrolled in the trial. No conclusion on race effect can be made because of the limited number of patients other than Caucasian race available in the study.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Drug established and trade name: Ferrlecit

Drug class: Intravenous iron products

Sponsor's proposed indication: Treatment of iron deficiency anemia in pediatric (ages 6-15 years) patients undergoing chronic hemodialysis who are receiving supplemental epoetin therapy.

Sponsor's proposed dose regimen: 0.12 mL/kg (1.5 mg/kg of elemental iron) diluted in 25 mL 0.9% sodium chloride and administered by intravenous infusion over 1 hour at eight sequential dialysis sessions.

B. State of Armamentarium for Indication(s)

Approved Products	Dosage and Administration	Population	Wording in indication
INFeD (iron dextran injection)	Adults and Children over 15 kg (33 lbs): Dose (mL) = 0.0442 (Desired Hb-Observed Hb) × LBW (kg) + (0.26 × LBW) Children 5-15 kg (11-33 lbs): Dose (mL) = 0.0442 (Desired Hb-Observed Hb) × W (kg) + (0.26 ×W) Each mL contains 50 mg of elemental iron. A test dose is required before the dosing.	Adults and Pediatrics	"treatment of patients with documented iron deficiency in whom oral administration is unsatisfactory or impossible"
Ferrlecit (sodium Ferric Gluconate complex in Sucrose injection)	125 mg of elemental iron intravenously (at a rate of up to 12.5 mg/min) over eight sessions at sequential dialysis by slow injection or infusion over 1 hour diluted in 100 mL of 0.9% sodium chloride.	Adults	"treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental epoetin therapy"
Venofer (iron sucrose injection)	100 mg of elemental iron intravenously during each dialysis for 10 sequential dialysis sessions by slow injection: at a rate of 1 mL (20 mg iron) undiluted solution per minute or	Adults	"treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental

	by infusion: over at least 15 minutes diluted exclusively in a maximum of 100 mL of 0.9% NaCl, immediately prior to infusion.		erythropoietin therapy"

Reviewer's table

C. Important Milestones in Product Development

Ferrlecit was approved on February 18, 1999 for treatment of iron deficiency anemia in adult patients undergoing chronic hemodialysis who are receiving supplemental epoetin therapy. The sponsor agreed to perform a study to determine the safe and effective dosing regimen in the pediatric population as one of the Phase 4 study commitments (NDA 20-955, Approval Letter, Phase 4 commitments: #5, dated 2/18/1999). The sponsor submitted initial Proposed Pediatric Study Request in January 1999, and revised protocol in November 2001. On August 9, 2002, the Agency issued a Written Request for Pediatric Study to the sponsor. In response the Written Request, the sponsor conducted a pediatric clinical study (FR01006) and was granted Pediatric Exclusivity on March 24, 2004.

D. Other Relevant Information

The proposed pediatric dosing regimen has not been approved in other countries.

E. Important Issues with Pharmacologically Related Agents

Intravenous iron products have been associated with anaphylactoid reactions. INFeD (iron dextran) has a black boxed warning for anaphylactic-type reactions. Ferrlecit and Venofer have warnings for hypersensitivity reaction.

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

No new data were submitted for Chemistry, Animal Pharmacology and Toxicology, and Microbiology.

See Biopharmaceutics and Statistics reviews.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

See Biopharmaceutics review.

B. Pharmacodynamics

See Biopharmaceutics review.

IV. Description of Clinical Data and Sources

A. Overall Data

The following material in the NDA submission was reviewed:

- NDA SE5-006 volume A68.1-A68.37, submitted February 13, 2004

B. Tables Listing the Clinical Trials

Studies	Type of trials	Number of patients enrolled	Dose regimens	Location of the study
FR01006	Multi-center, randomized, double-blind, parallel group, dose-response study	67 pediatric patients with age 6-15 years who were undergoing chronic hemodialysis	Treatment A: Ferrlecit 1.5 mg/kg Treatment B: Ferrlecit 3.0 mg/kg. Infused by syringe pump over 1 hour, not to exceed 125 mg per dose, during 8 consecutive dialysis sessions over 22 days	United States, Mexico, Poland, Russia, and Serbia

Reviewer's table

C. Postmarketing Experience

Ferrlecit was approved on February 18, 1999 in U.S. and has been marketed in Europe for more than 40 years.

D. Literature Review

No literature review was provided by the sponsor.

V. Clinical Review Methods

A. How the Review was Conducted

One clinical trial was submitted and was reviewed for the proposed new pediatric dosing regimen. The trial and other submitted material were evaluated in the integrated safety summary.

B. Overview of Materials Consulted in Review

The datasets of the one study submitted were examined for the efficacy and safety evaluation.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

No inspection was done for this supplement.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trial was conducted in accordance with accepted ethical standards. Written informed consents were required from all legally authorized representatives of pediatric patients in the trial. Independent ethics committees/institutional review boards at all participating centers were required to give permission for these studies.

E. Evaluation of Financial Disclosure

The sponsor certified that there was no financial arrangement with clinical investigators, who conducted the clinical trial (Form FDA 3454).

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Study FR01006 showed significant increases from baseline in hemoglobin at 2 weeks after treatment in both dosing groups (0.8 g/dL in the 1.5 mg/kg group and 0.9 g/dL in the 3.0 mg/kg group) and the effect was maintained at 4 weeks after treatment. There was no significant difference in efficacy between the 1.5 mg/kg and 3.0 mg/kg dosing regimens.

B. General Approach to Review of the Efficacy of the Drug

The sponsor has submitted one study (FR01006) to support the new dose regimen for pediatric patients. This study was reviewed in detail.

C. Detailed Review of Trials by Indication

One trial was conducted to support the new dose regimen for the treatment of iron deficiency anemia in pediatric patients who are undergoing chronic hemodialysis.

Study Protocol

Title of the Study

A Randomized, Double-Blind, Parallel Group, Multi-Center Study of the Efficacy of Two Doses of Ferrlecit in the Treatment of Iron Deficiency in Pediatric Hemodialysis Patients Receiving Epoetin.

Study Objectives

Primary Objectives

The primary objective of this study was to demonstrate and compare the effectiveness of two Ferrlecit doses in increasing hemoglobin in iron-deficient pediatric HD patients undergoing repletion Ferrlecit therapy.

Secondary Objectives

The secondary objectives of this study were:

- To evaluate the single-dose pharmacokinetics of Ferrlecit in iron deficient pediatric HD patients, and
- To assess the safety profile of Ferrlecit in pediatric HD patients.

Study Design

This was a multicenter, randomized, double-blind, dose-response (two doses), and parallel-group study in pediatric patients undergoing chronic hemodialysis who are receiving erythropoietin therapy. A subset of patients at select study centers participated in a single-dose pharmacokinetics study.

Study Patients

The study was to enroll at least 29 chronic HD pediatric patients with ESRD on stable erythropoietin (EPO) therapy in each dosing group (up to 58 patients total) who meet the eligibility criteria listed below.

Inclusion Criteria:

- Male or female pediatric ESRD patients ≥ 2 and ≤ 15 years of age whose legally authorized representative provided signed informed consent;
- TSAT < 20% and/or serum ferritin < 100 ng/mL (at Screening Visit 5 or at the last re-screening visit);
- Receiving chronic HD therapy with an identified need for repletion iron therapy;
- Receiving a stable EPO dosing regimen (defined as no greater than a 25% change in the patients EPO dose during the 4 weeks before Screening Visit 5);
- Negative serum pregnancy test (female patients of childbearing potential only).

Exclusion Criteria:

- Receipt of any form of iron supplementation during the 4 weeks prior to the first Ferrlecit dosing;
- Blood transfusion within the 4 weeks before Ferrlecit dosing or at any time during the study;
- Hypersensitivity to Ferrlecit or any of its inactive components;
- Significant inflammatory conditions;

- Pregnant or lactating female;
- Clinical instability defined as:
  - Serum albumin < 2.5 g/dL;
  - Signs or symptoms of current severe infection;
  - Active malignancy;
  - Blood sugar > 300 mg% or < 50 mg% at any point in preceding 3 weeks;
  - Inability to achieve adequate dialysis (adequacy is defined as a single pool Kt/V = 1.2 or an average urea reduction ratio [URR] of at least 65%).
- Use of an investigational agent within 30 days prior to the predicted date of first dosing.

Study Treatment

Patients meeting the requirements of iron deficiency at the end of the 4 week screening period (or the re-screening period) were to be randomized to one of the following two treatment groups:

Treatment A:
Ferrlecit 1.5 mg/ kg, infused intravenously by syringe pump over 1 hour, not to exceed 125 mg per dose, during eight consecutive HD sessions over an approximate 22 day period, or

Treatment B:
Ferrlecit 3.0 mg/kg, infused intravenously by syringe pump over 1 hour, not to exceed 125 mg per dose, during eight consecutive HD sessions over an approximate 22 day period.

Each Ferrlecit infusion was to begin between 1 and 2 hours after dialysis had begun and when the patient was clinically stable.

Ferrlecit was supplied as a deep red, sterile liquid complex of ferric sodium gluconate in sucrose for intravenous injection, in 5 mL single dose ampules, each ampule containing 62.5 mg of elemental iron (12.5 mg/ mL). Each mL also contained 9 mg of benzyl alcohol as an inert ingredient.

Therapeutic infusions of Ferrlecit were prepared by an unblinded, qualified individual at each clinical site. Following preparation of each patient's required Ferrlecit dose by the unblinded individual, the administration syringe was covered with an opaque material and the syringe taken to the hemodialysis unit. Blinding was to be maintained throughout the study.

Prior and Concomitant Therapy

The patients maintained their normal dialysis treatment regimen during the screening phase, the Ferrlecit administration phase, and the follow-up phase of the study.

There were no restrictions on concomitant medications, except for investigational agents which the patient could not use within 30 days before the start of the first screening visit or during the course of the study, and any oral or intravenous iron containing products, other than Ferrlecit, during the 4-week period before the date of the anticipated first Ferrlecit dose, or any iron

supplement other than Ferrlecit per protocol during the study period. Concomitant medications were documented and updated in the CRFs at each clinic visit.

Efficacy Endpoints

Primary efficacy endpoint

The primary efficacy endpoint was the change in Hgb from baseline (defined as the Hgb value at Screening Visit 5 or, if applicable, the Hgb value at the last re-screening visit) to 2 weeks following the last study drug administration.

Secondary efficacy endpoints

Secondary efficacy endpoints were the change in Hct, TSAT, serum ferritin, CHr, and HCRBC from baseline to 2 weeks after the last study drug administration.

Pharmacokinetic Parameters

A subset of clinical sites participated in the determination of the single-dose pharmacokinetics of Ferrlecit. The pharmacokinetics of Ferrlecit-bound iron (calculated as total iron minus transferrin-bound iron) was determined in all iron-deficient patients who consented to this additional procedure immediately following the start of the patient's first Ferrlecit administration. Blood samples (2 mL/sample) for the measurement of total iron and transferrin-bound iron were collected within 5 minutes before the start of the patient's first Ferrlecit administration and at 30, 60, 75, 90, 120, 180, 240, and 360 minutes after the start of the first Ferrlecit administration. One additional blood sample was obtained 48 hours after the start of the first Ferrlecit infusion (i. e., immediately prior to the second Ferrlecit infusion).

The single-dose pharmacokinetics of Ferrlecit-bound iron will be described by the following pharmacokinetic variables: AUC_{0-t}, $AUC_{0-\infty}$, Cl, C_{max}, k_{el}, $t_{1/2}$, T_{max}, and V_d.

Study Plan

The study consisted of a 4 (or potentially 5) week Screening Period, an approximately 22 day repletion treatment period during which the patient was on a fixed and stable HD schedule, an evaluation of efficacy parameters 2 weeks after administration of the final Ferrlecit dose, and a final evaluation 4 weeks after administration of the final Ferrlecit dose.

The sponsor’s schedule of events is presented below.

Table 9.5-1 Treatment schedule of events

Procedure	Screening Period						Ferrlecit Infusion Period			Post Infusion Period	
							Visits 1 through 8			Visit 9	Visit 10
	SV1*	SV2	SV3	SV4	SV5	RSV[1]	Dose 1	Doses 2-7	Dose 8	14 Days After Final Dose	28 Days After Final Dose
Informed Consent	X										
Medical History	X										
Phys Exam Incl Vital Signs	X										
Concomitant Medication	X						X	X	X	X	
Discontinue Iron Supplementation	X										
Final Eligibility Assessment							X[3]				
Randomization							X				
Hgb[2]	X	X	X	X	X	X				X	X
Hct, serum ferritin, TSAT[2]	X				X	X				X	X
Body Weight for Ferrlecit Dose Determination					X	X					
CHr and HCRBC[2]					X					X	X
Safety Labs[2]	X									X	
Blood Sample for Extra Hgb Determination		X	X	X							
Ferrlecit® Administration							X	X	X		
Vital Signs[5]							X	X	X		
AE Assessment							X	X	X	X	X

* SV = screening visit

[1] Re-screening visit(s) (RSV) were optional

[2] Safety and efficacy labs were assessed immediately, if possible or if permitted, whenever a patient lost eligibility (*e.g.*, transplantation) or withdrew consent.

[3] Final study eligibility was based on the serum ferritin and TSAT values obtained at Screening Visit 5 or at the re-screening visit.

[4] Refer to Table 9.5-2 for details of the pharmacokinetic portion of the study.

[5] Blood pressure and pulse were recorded as detailed in Section 9.5.1.4.

Sponsor's table in NDA/SE5-006 submission FR01006 study report Table 9.5-1.

Safety Assessment

Safety measurements included the incidence and severity of adverse events, clinical laboratory abnormalities, serum pregnancy test (for females of childbearing potential only), physical examinations, and vital signs.

Adverse events were assessed from the time of first study drug administration until exit from the study. In particular, patients were observed during and shortly after each Ferrlecit infusion for the occurrence of hypotension and non-anaphylactic allergic or anaphylactic reactions. The following definitions of hypotension, non- anaphylactic allergic reaction, and anaphylactic reaction were supplied to each study site:

- Hypotension – systolic blood pressure < 90 mm Hg or a decrease of > 40 mm Hg from the starting systolic blood pressure and which may be associated with such events as syncope, light-headedness, nausea, or sweating;

- Non-Anaphylactic Allergic Reaction – an allergic reaction which may be associated with rash, pruritis, cramps, abdominal or other acute spasmodic pain, nausea, or vomiting;
- Anaphylactic Allergic Reaction – a life-threatening event that takes place within seconds to minutes following exposure to an allergen (e. g., drug), manifestations of which may include pruritis, urticaria, angioedema, broncospasm, laryngeal edema, nausea, vomiting, abdominal pain, hypotension, arrhythmias, or vascular collapse.

At every study visit, patients (or a legal guardian if the patient was too young to comprehend the question) were asked a standard question to elicit any medically related changes in their well being. They were also asked if they had been hospitalized, had any accidents, used any new medications, or changed any concomitant medication regimens (both prescription and over- the-counter medications).

Statistical Methods

Analyzed population

- Safety population: defined as all patients who were exposed to study medication.
- Completer population: defined as all patients who completed Ferrlecit administrations, had no major protocol deviations, and provided data for the 2 weeks after the last Ferrlecit administration visit.

Efficacy analysis
The primary efficacy endpoint was the change in Hgb from baseline to 2 weeks following the final Ferrlecit administration. The baseline visit was defined as Screening Visit 5 or, if applicable, the re-screening visit. A significant difference between the Ferrlecit treatment groups for the change from baseline to 2 weeks following the final Ferrlecit infusion in Hgb was tested using a two-sample t-test for the Completer population.

In addition, significant differences from zero in the change in Hgb from baseline to 2 weeks following the final Ferrlecit infusion was tested using paired t-tests for each Ferrlecit treatment separately for the Completer population.

A clinically significant change from baseline in Hgb was defined as 1.0 g/dL. Conclusions of significant changes from baseline were drawn when the changes were both statistically significant and clinically significant.

Secondary efficacy endpoints were the changes in Hct, TSAT, serum ferritin, HCRBC, and CHr from baseline to 2 weeks following the final Ferrlecit administration. Additionally, patients were classified as responders to treatment if they had an increase in Hgb of at least 1.0 g/dL. The secondary efficacy endpoint of responder/non-responder was assessed at 2 weeks following the final Ferrlecit administration.

Safety analysis

The incidence of treatment-emergent AEs was summarized using the Safety population. AEs were coded using COSTART terminology.

Determination of sample size
The sample size estimation was made based on using a paired t-test to detect a significant difference from zero for the change from baseline in Hgb. Assuming a standard deviation of differences in Hgb of 1.61 g/dL, a minimum of 23 patients per dose group were to be needed to detect a significant difference for a change in Hgb from baseline of 1.0 g/dL with 80% power at α= 0.05. Using the same assumptions as described above, 30 patients per dose group were to be needed to detect a significant difference for a change in Hgb from baseline of 1.0 g/dL with 90% power at α= 0.05.

A sufficient number of patients needed to detect a significant difference in the primary efficacy determination (approximately n=29 per dose group) was to be targeted for enrollment into the study.

Changes in the Conduct of the Study or Planned Analyses

There were three amendments to the protocol, dated August 1, 2002, September 6, 2002, and December 5, 2002.

Amendment 1:
The following revisions were made to the protocol:

- One additional blood draw for the evaluation of Ferrlecit-bound iron was added;
- The pharmacokinetic analysis was revised to incorporate the additional sampling time and to apply a population pharmacokinetic model for Ferrlecit-bound iron that was previously developed for adults to the pediatric population;
- The method for obtaining body temperature was revised to allow for methods other than oral.

Amendment 2:
The following revisions were made to the protocol:

- Additional study centers in Eastern Europe and Mexico were added to the study. The Study Administrative Structure was therefore revised to indicate the Contract Research Organization responsible for the monitoring of these sites and the location of the central laboratory that the Eastern European sites will use;
- The method of administering Ferrlecit was changed from "infusion" to "infusion by syringe pump";
- Per FDA request, one additional blood draw for the evaluation of efficacy parameters 4 weeks after the final Ferrlecit infusion, was added;
- Per FDA request, the upper age limit for eligibility was reduced from 16 years to 15 years of age;

- The statistical analysis was revised to accommodate an additional blood sample and age change, and to include additional analyses requested by the FDA;
- The exclusion criteria concerning any hospitalizations 30 days before study initiation was removed;
- The patient was no longer required to be in a fasted state when providing blood samples during the screening visit for the evaluation of clinical chemistries and hematology;
- The procedure for diluting the Ferrlecit solution prior to infusion was revised.

Amendment 3:
The following revisions were made to the protocol:

- The overall study design was revised to allow patients who were not iron deficient at Screening Visit 5 to re- screen 1 week later rather than re- starting the entire screening process. This was done to minimize the time during which the patient was not to receive supplemental iron therapy or change their erythropoietin dose by more than ± 25%;
- The inclusion criteria specifying the time frame during which adjustments to the patients erythropoietin dose may occur was reduced from 8 weeks before obtaining Informed Consent to 4 weeks prior to Screening Visit 5;

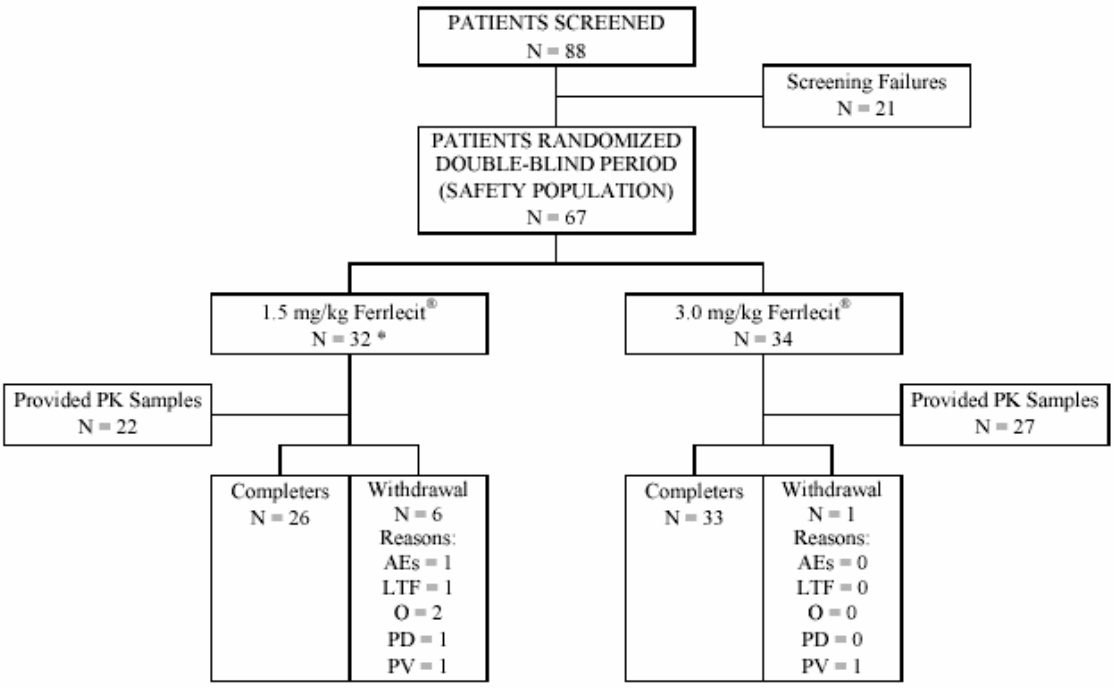
Study Patients

Disposition of Patients

A total of 88 patients were screened, 67 were enrolled and randomized at 21 sites from 5 countries. One patient was withdrawn from study due to kidney transplantation after being randomized (to the 1.5 mg/ kg treatment group) but prior to receiving any study medication. A total of 66 patients received study drug in the study (32 in the 1.5 mg/kg group and 34 in the 3.0 mg/kg group).

Among 66 patients who received study drug, 7 (10.6%) patients discontinued treatment prematurely (2 due to protocol violations, 2 for other reasons, 1 due to an adverse event, 1 lost to follow up, and 1 withdrew voluntarily). A total of 59 (89%) patients completed the study treatment. See the following chart.

Figure 10.1-1: Patient disposition flow chart.



* One patient withdrew from the study after randomization but prior to receiving study drug due to kidney transplantation reducing the number of patients participating in the 1.5 mg/kg froup from 33 to 32.

Reasons for discontinuation: AE = adverse event, LTF = lost to follow-up; O = other; PD = patient decision; PV = protocol violation

Source: Section 14, Table 14.1-2; Appendix 16.2, Listing 16.2.1-1

Sponsor's table in NDA/SE5-006 submission FR01006 study report Figure 10.1-1.

The following table shows the patient enrollment by country and center. A total of 26 centers initially participated in the study, 23 centers screened patients for the enrollment, and 21 centers actually enrolled patients in the study. A total of 66 patients received at least one dose of Ferrlecit (safety population), 57 patients completed Ferrlecit treatment and had hemoglobin value available at 2 weeks after the last dose of Ferrlecit administration (completer population), and 49 patients had blood samples available for PK analysis.

Patient enrollment summary by country

Country	Safety Population N = 66	Completer Population N = 57	PK Participants N = 49
All countries (26/23/21)*	**66**	**57**	**49**
1.5 mg/kg Ferrlecit	32	25	22
3.0 mg/kg Ferrlecit	34	32	27
Mexico (2/2/1)*	**5**	**4**	**3**
1.5 mg/kg Ferrlecit	2	1	1
3.0 mg/kg Ferrlecit	3	3	2
Poland (9/9/8)*	**16**	**13**	**15**
1.5 mg/kg Ferrlecit	6	5	6

3.0 mg/kg Ferrlecit	10	8	9
Russia (6/6/6)*	**20**	**19**	**18**
1.5 mg/kg Ferrlecit	9	8	8
3.0 mg/kg Ferrlecit	11	11	10
Serbia (1/1/1)*	**8**	**7**	**8**
1.5 mg/kg Ferrlecit	4	3	4
3.0 mg/kg Ferrlecit	4	4	4
United States (8/5/5)*	**17**	**14**	**5**
1.5 mg/kg Ferrlecit	11	8	3
3.0 mg/kg Ferrlecit	6	6	2

* number of sites: participated /screened patients /randomized patients
Sponsor's table in NDA/SE5-006 submission FR01006 study report Table 10.1-1.

Protocol Deviations

Nine patients were excluded from the Completer population because of protocol violation; seven from the 1.5 mg/kg Ferrlecit treatment group and 2 from the 3.0 mg/kg Ferrlecit treatment group. The following table summarizes reasons for exclusion by treatment group.

Reasons for patient exclusion from Completer population

Reason for exclusion from Evaluable population*	**1.5 mg/kg Ferrlecit N = 32**	**3.0 mg/kg Ferrlecit N = 34**
Missing 2 week post final Ferrlecit dose data	5	1
Major Protocol Deviation: Dosing Compliance (did not receive all required Ferrlecit infusions)	4	2
Major Protocol Deviation: Excluded Medication	1	1
Major Protocol Deviation: Lost to Follow Up	1	0
Major Protocol Deviation: Adverse Event (Kidney Transplant)	1	0
Number of patients in completer population	25	32

* Some patients had more than one reason for exclusion
Sponsor's table in NDA/SE5-006 submission FR01006 study report Table 11.1-2.

One major protocol deviation with regards to the pharmacokinetic portion of the study occurred in 1 patient. The patient's final blood draw occurred 24 hours late.

Demographic and Other Baseline Characteristics

Demographics

Patients participating in the study were pediatric patients diagnosed with End Stage Renal Disease requiring regular HD 2 to 4 times per week. The mean age of the patients was 12.1 ± 2.6 years. There were similar numbers of male and female patients in the study. The majority of patients were of white ethnicity with small numbers of Hispanic, Asian, and Black.

The following Table summarizes patient demographics and baseline characteristics for the Safety population.

Patient demographics (safety population)

Characteristic	1.5 mg/kg Ferrlecit N = 32	3.0 mg/kg Ferrlecit N = 34	Overall N = 66
Gender (N, %)			
Female	17 (53.1%)	15 (44.1%)	32 (48.5%)
Male	15 (46.9%)	19 (55.9%)	34 (51.5%)
Race (N, %)			
White	21 (65.6%)	26 (76.5%)	47 (71.2%)
Black	1 (3.1%)	3 (8.8%)	4 (6.1%)
Hispanic	8 (25.0%)	4 (11.8%)	12 (18.2%)
Asian	1 (3.1%)	0 (0.0%)	1 (1.5%)
Other	1 (3.1%)	1 (2.9%)	2 (3.0%)
Age (years)			
Mean±SD	12.3 (2.5)	12.0 (2.6)	12.1 (2.6)
Median	12.9	12.1	12.4
Range	6.7 - 15.7	6.1 - 15.9	6.1 - 15.9
Age (N, %)			
2- 5 years	0 (0.0%)	0 (0.0%)	0 (0.0%)
6-12 years	16 (50.0%)	22 (64.7%)	38 (57.6%)
13- 15 years	16 (50.0%)	12 (35.3%)	28 (42.4%)
Height (cm)			
Mean ±SD	138.6 (20.3)	135.4 (19.3)	137.0 (19.7)
Median	136.8	135.0	135.5
Range	98.0 - 183.0	104.0 - 177.5	98. - 183.0
Weight (kg)			
Mean ± SD	37.7 (19.9)	32.5 (12.4)	35.0 (16.6)
Median	36.1	28.7	32.2
Range	16.3 - 115.0	15.2 - 63.2	15.2 - 115.0

Sponsor's table in NDA/SE5-006 submission FR01006 study report Table 11.2-1.

Reviewer's comments: Although patients 2 to 15 years of age were eligible for the study, no patients 2 to 5 years of age were enrolled due to scarcity of patients in this age range. The incidence of end-stag renal disease in patients younger than 5 years was 9 per million annually based on end-stage renal disease registries (The USRDS and its products- United States Renal Data System, VIII. Pediatric end-stage renal disease, Am J Kidney Dis 1998: pp S98-108).

Hemoglobin level

Assessment repeated measurements of Hgb were taken during the 5 screening visits (SCV) prior to randomization. The results of these measurements are shown below. The mean Hgb was about 9 g/dL in these 5 screening visits and the overall mean was 9.4 g/ dL.

Hgb levels by screening visit

	SCV 1	SCV 2	SCV 3	SCV 4	SCV 5	Re-screen	Overall

Mean (± SD)	9.2 (2.1)	9.4 (2.4)	9.3 (2.2)	9.5 (2.2)	9.6 (2.2)	8.9 (1.9)	9.4 (2..2)
Range	5.0 – 13.6	4.7 – 14.7	4.9 – 14.5	4.6 – 13.8	5.2 – 14.1	5.4 – 11.7	4.6 – 14.7
N	57	57	57	53	56	11	291

Sponsor's table in NDA/SE5-006 submission FR01006 study report Table 11.4-1.

Medical History

Concurrent medical history was similar between treatment groups. The majority of patients had a history of hematologic (97%), cardiovascular (83%), musculoskeletal (56%), and gastrointestinal (52%) diseases.

Concomitant Medications

The majority of patients were taking medications at study entry for medical conditions typically occurring in this patient population. Concomitant medications during the study treatment included antianemic preparations (100%), calcium channel blockers (50.0%), agents acting on the renin-angiotensin system (37.9%), antithrombotic agents (36.4%), antibacterials for systemic use (31.8%), and beta blocking agents (25.8%). Similar medications were used in patients prior to randomization. There were no significant differences in concomitant medications between the two treatment groups.

Two (3%) patients (1 in each group) received an excluded medication (packed red blood cells) during the study treatment and were discontinued from further study participation at that time.

All patients were on stable erythropoietin (EPO) dose (defined as no greater than a 25% change in dose during the 4 weeks before Screening Visit 5) for at least 4 weeks prior to infusion of their first Ferrlecit dose. Seven instances of a change in a patient's EPO dose during the course of the study occurred (see Table below). The EPO dose of all other patients remained constant throughout the duration of the study.

Erythropoietin dose changes during the study

Patient #	First Ferrlecit Dose	Last Ferrlecit Dose	Visit 9 Date	Date of EPO Change	Initial EPO Dose	Changed EPO Dose
0101	09 Sep, 2003	25 Sep, 2003	09 Oct, 2003	13 Oct, 2003	2000 U/HD Session	1000 U/HD
0204	14 Jul, 2003	30 Jul, 2003	13 Aug, 2003	15 Aug, 2003	2500 U/HD Session	2000 U/HD
0301	16 Apr, 2003	02 May, 2003	16 May, 2003	05 May, 2003	2800 U/HD Session	2400 U/HD
1307	14 Apr, 2003	30 Apr, 2003	14 May, 2003	21 Apr, 2003	5500 U2x/week	5500 U 3x/week
2502	01 Sep, 2003	10 Sep, 2003	--*	*	3000 U3x/week	*
4505	28 Apr, 2003	14 May, 2003	28 May, 2003	02 Jun, 2003	6000 U/week	2000 U/week
4506	28 Apr, 2003	14 May, 2003	28 May, 2003	02 Jun, 2003	4000 U/week	2000 U/week

* Patient 2502's EPO dose was increased or decreased by 33% on multiple occasions during the study. The patient was withdrawn from study participation prior to study visit 9 after being administered an excluded medication.

Sponsor's table in NDA/SE5-006 submission FR01006 study report Table 10.3-4.

In four of the seven instances, the EPO dose was decreased after the 2 week post-final Ferrlecit infusion visit and would therefore have no effect on the final efficacy parameters. The EPO dose of one patient was changed after infusion of the final Ferrlecit infusion but before the 2 week post-final Ferrlecit infusion visit. The EPO dose of one patient was inadvertently changed at HD session 4 (Ferrlecit infusion 4) from 5500 U, twice a week to 5500 U, three times a week where

it then remained for the duration of the study. The data from this patient were excluded from the analysis of efficacy. The EPO dose of one patient was adjusted upward by 25% during the screening visit from 3000 U, three times a week to 3750 U, three times a week. During the treatment phase of the study, this patient's EPO dose was changed on multiple occasions from 3750 U, three times a week to 3000 U daily, to 4000 U daily, and then back and forth between 3000 daily U and 4000 daily U. The patient was withdrawn from further study participation after the fifth Ferrlecit dose for receipt of an excluded medication. The efficacy data from this patient was excluded from the analysis of efficacy.

Efficacy Evaluation

Efficacy results are presented for the Completer population. The following table shows the number of patients in each analyzed population.

Number of patients in each population

Population	1.5 mg/kg Ferrlecit	3.0 mg/kg Ferrlecit	Overall
Safety	32	34	66
Completer	25	32	57
Pharmacokinetic	22	27	49

Sponsor's table in NDA/SE5-006 submission FR01006 study report Table 11.1-1.

Primary Efficacy Endpoint

The primary efficacy endpoint was mean change from baseline in Hgb level at 2 weeks after the last Ferrlecit treatment. The results showed that the mean change from baseline in Hgb was 0.8 g/ dL in the Ferrlecit 1.5 mg/kg treatment group and 0.9 g/dL in the Ferrlecit 3.0 mg/ kg treatment group. This rise in mean Hgb concentrations was maintained for at least 2 additional weeks, and increased to 1.0 g/dL in the 3.0 mg/kg treatment group. The Hgb change was not statistically different at 2 weeks after the final Ferrlecit infusion between the two treatment groups ($p = 0.75$).

As compared to baseline, hemoglobin at 2 weeks after the last Ferrlecit treatment increased significantly in both treatment groups ($p = 0.0033$ in the 1.5 mg/kg treatment group and $p < 0.0001$ in the 3.0 mg/kg treatment group).

The following table shows the primary efficacy results.

Hgb (g/dL) response and its change from baseline (completer population)

Time of Evaluation	Statistic	1.5 mg/kg Ferrlecit N = 25		3.0 mg/kg Ferrlecit N = 32	
		Value	Change From Baseline	Value	Change From Baseline
Baseline	Mean (SD)	9.7 (2.1)		9.4 (2.3)	
	Range	5.2 - 14.1		5.4 - 13.0	
	n	25		32	
2 Weeks After Final Ferrlecit Infusion	Mean (SD)	10.6 (2.2)	0.8 (1.30)	10.4 (2.1)	0.9 (1.12)
	Range	5.8 - 13.9	-1.0 - 4.0	5.1 - 14.1	-2.2 - 3.1
	n	25	25	32	32
	P-Value *	0.0033		<0.0001	
	P-Value **	0.7547			
4 Weeks After Final Ferrlecit Infusion	Mean (SD)	10.7 (2.2)	0.9 (1.67)	10.5 (2.3)	1.0 (1.56)
	Range	6.1 - 15.0	-2.1 - 5.0	4.2 - 13.7	-1.8 - 4.8
	n	24	24	32	32

*P-value calculations based on a paired t-test with the null hypothesis that the change from baseline equals 0.
**P-value calculations based on a two-sample t-test with the null hypothesis of no difference between dose groups.
Sponsor's table in NDA/SE5-006 submission FR01006 study report Table 11.4-2.

Reviewer's comments: The results using the Safety population were similar to those using the Completer population by the sponsor. The mean change in hemoglobin was 0.7 g/dL in the 1.5 mg/kg group and 0.8 g/dL in the 3.0 mg/kg group with a significant increase in each group as compared to baseline (p=0.0049 and 0.0002, respectively). There was no significant difference in change in hemoglobin between the two dosing groups (p=0.4802). See table below.

Hgb (g/dL) response and its change from baseline (Safety population)

Time of Evaluation	Statistic	1.5 mg/kg Ferrlecit N = 29		3.0 mg/kg Ferrlecit N = 34	
		Value	Change From Baseline	Value	Change From Baseline
Baseline	Mean (SD)	9.8 (2.3)		9.4 (2.3)	
2 Weeks After Final Ferrlecit Infusion	Mean (SD)	10.6 (2.4)	0.7 (1.34)	10.2 (2.2)	0.8 (1.10)
	P-Value *	0.0049		0.0002	
	P-Value **	0.4802			

*P-value using signed rank test for comparison in changes in hemoglobin between 2-weeks after final Ferrlecit infusion and baseline in each dosing group calculated by Dr. Milton C. Fan, Ph.D.
**P-value using singed rank test for comparison in changes in hemoglobin between two dose groups calculated by Dr. Milton C. Fan, Ph.D.
Reviewer's table.

Secondary Efficacy Endpoints

Response

Response to therapy was defined as an increase in Hgb concentration of at least 1 g/dL at two weeks after the last Ferrlecit infusion from the baseline. The response rate was 40% in the 1.5 mg/kg Ferrlecit group and 50% in the 3.0 mg/kg group. There was no statistically significant difference in the response rate between the two treatment groups (p= 0.4519).

Summary of responders and non- responders to treatment

	Statistic	**1.5 mg/kg Ferrlecit N = 25**	**3.0 mg/kg Ferrlecit N = 32**
2 Weeks After Final Ferrlecit Infusion	Response (n, %)	10 (40%)	16 (50%)
	Non-response (n, %)	15 (60.0%)	16(50%)
	P-value *	0.4519	

*P-value is calculated using the normal approximation to the Chi-square test based on the null responders equals 0.5.
Sponsor's table in NDA/SE5-006 submission FR01006 study report Table 11.4-3.

Reviewer's comments: The results were similar when using the Safety population. See table below.

Summary of responders and non- responders to treatment

	Statistic	**1.5 mg/kg Ferrlecit N = 29**	**3.0 mg/kg Ferrlecit N = 34**
2 Weeks After Final Ferrlecit Infusion	Response (n, %)	11 (38%)	16 (47%)
	P-value *	0.4656	

*P-value is calculated using the Exact test by Dr. Milton C. Fan, Ph.D.
Reviewer's table.

Hct, TSAT, Serum Ferritin, CHr, and HCRBC

There was no difference in mean changes in Hct from baseline between the 3.0 mg/kg and 1.5 mg/kg treatment groups (3.0% and 2.6%, respectively, p=0.54). However, the mean increase from baseline in ferritin level was statistically significantly higher in the 3.0 mg/kg group as compared to the 1.5 mg/kg group (257 ng/mL and 192 ng/mL, respectively, p=0.0003). The mean increase in TSAT from baseline was borderline significant in the 3.0 mg/kg group as compared to the 1.5 mg/kg group (10.5% and 5.5%, respectively, p=0.08). There was no statistically significant difference between the two treatment groups in CHr and HCRBC (p=0.90 and p=0.88, respectively).

Statistically significant increases in Hct, TSAT, serum ferritin, and CHr concentrations from baseline were observed at 2 weeks after the last Ferrlecit infusion in both the 1.5 mg/kg and 3.0 mg/kg treatment groups. Increases in Hct, TSAT, serum ferritin, and CHr concentrations were maintained for an additional 2 weeks, and for TSAT and serum ferritin, the mean concentrations continued to increase for the duration of the study. There was no significant change in HCRBC from baseline in either treatment group.

The following table shows the mean change in Hct, TSAT, serum ferritin, CHr, and HCRBC from baseline.

Change in secondary efficacy variables from baseline to endpoint

Time of Evaluation	Statistic	1.5 mg/kg Ferrlecit N = 25		3.0 mg/kg Ferrlecit N = 32	
		Value	Change From Baseline	Value	Change From Baseline
	Hct (%)				
Baseline	Mean (SD)	29.3 (6.9)		28.4 (6.8)	
	Range	15.0, 44.2		16.7, 39.6	
	n	25		32	
2 Weeks After Final Ferrlecit® Infusion	Mean (SD)	31.9 (6.6)	2.6 (3.9)	31.4 (6.5)	3.0 (3. 7)
	Range	17.0 - 41.6	-3.9 - 10.9	15.5 - 44.5	-5.0 - 15.8
	n	25	25	32	25
	P-Value *	0.0031		<0.0001	
	P-Value **	0.5357			
4 Weeks After Final Ferrlecit® Infusion	Mean (SD)	32.2 (6.5)	2.4 (5.4)	31.2 (6.7)	2.7 (4.1)
	Range	18.0, 44.3	-6.8, 14.9	12.8, 42.5	-5.3, 10.9
	n	24		32	
	TSAT (%)				
Baseline	Mean (SD)	19.8 (10.3)		16.2 (10.6)	
	Range	5.0, 47.0		2.0, 50.0	
	n	24		32	
2 Weeks After Final Ferrlecit® Infusion	Mean (SD)	24.9 (12.9)	5.5 (11.0)	26.7 (16.4)	10.5 (14.0)
	Range	6.0 - 51.3	-15.0 - 34.4	0.3 - 75.6	-14.0 - 61.1
	n	25	25	32	32
	P-Value *	0.0096		<0.0001	
	P-Value **	0.0792			
4 Weeks After Final Ferrlecit® Infusion	Mean (SD)	27.8 (17.0)	9.0 (15.3)	24.9 (14.9)	8.7 (11.8)
	Range	9.7 - 94.9	-13.0 - 64.0	0.5 - 69.5	-15.0 - 47.0
	n	24	24	32	32
	Serum Ferritin (ng/ml)				
	Mean (SD)	87.8 (120.1)		161.8 (223.5)	
Baseline	Range	10.0, 574.6		0.0, 804.8	
	n	25		32	
2 Weeks After Final Ferrlecit® Infusion	Mean (SD)	279.6 (327.2)	191.8 (272.7)	475.9 (301.1)	314.0 (187.7)
	Range	50.5 – 1302.0	31.4 - 1229.9	85.6 – 1118.0	-23.0 - 767.0
	n	25		32	
	P-Value *	<0.0001		<0.0001	
	P-Value **	0.0003			
4 Weeks After Final Ferrlecit® Infusion	Mean (SD)	283.0 (338.0)	192.3 (287.1)	419.4 (336.5)	257.6 (159.7)
	Range	43.0 – 1290.0	-0.1 - 1217.9	28.0 – 1231.8	-28.0 - 608.0
	n	24	24	32	32
	CHr (pg)				
Baseline	Mean (SD)	31.2 (2.7)		31.0 (2.9)	
	Range	22.9, 35.4		22.5, 36.4	

	n	24		29	
2 Weeks After Final Ferrlecit® Infusion	Mean (SD)	32.4 (2.4)	1.3 (2.1)	32.1 (2.2)	1.2 (2.7)
	Range	27.3 - 37.7	-3.9 - 4.8	25.3 - 36.3	-5.7 - 7.3
	n	24	29	31	31
	P-Value *	0.0079		0.0297	
	P-Value **	0.9042			
4 Weeks After Final Ferrlecit® Infusion	Mean (SD)	32.1 (2.0)	1.0 (1.8)	32.1 (1.7)	1.0 (2.2)
	Range	26.0 - 35.3	-1.3 - 5.7	29.0 - 35.7	-5.0 - 7.6
	n	24	24	31	31
	HCRBC (%)				
Baseline	Mean (SD)	9.0 (10.8)		7.6 (10.7)	
	Range	0.4 - 40.3		0.4 - 43.9	
	n	24		29	
2 Weeks After Final Ferrlecit® Infusion	Mean (SD)	9.3 (12.8)	0.3 (8.0)	7.3 (9.4)	-1.4 (9.0)
	Range	0.8 - 43.8	-19.3 - 22.3	0.4 - 37.7	-24.0 - 22.9
	n	24	24	31	31
	P-Value *	0.6502		0.8701	
	P-Value **	0.8796			
4 Weeks After Final Ferrlecit® Infusion	Mean (SD)	13.7 (19.1)	4.9 (20.7)	7.1 (8.1)	-1.3 (6.9)
	Range	0.4 - 61.0	-23.8 - 59.9	0.6 - 31.7	-20.2 - 10.6
	n	24	24	31	31

*P-value calculations based on a paired t-test with the null hypothesis that the change from baseline equals 0.
**P-value calculations based on a two-sample t-test with the null hypothesis of no difference between dose groups.
Sponsor's table in NDA/SE5-006 submission FR01006 study report Table 11.4-4.

Reviewer's comments: The results of secondary efficacy endpoints based on the safety population were similar to those based on the completer population. There were significant increases in Hct, TSAT, ferritin and CHr at 2 weeks after the last Ferrlecit administration as compared to baseline at both dosing groups. Only ferritin showed a dose-response; it was significantly greater in the higher dosing group (3.0 mg/kg) than the lower dosing group (1.5 mg/kg). See table below.

Change in secondary efficacy variables from baseline to 2 weeks after last Ferrlecit infusion in Safety Population

Time of Evaluation	**Statistic**	**1.5 mg/kg Ferrlecit N = 25**		**3.0 mg/kg Ferrlecit N = 32**	
		Value	**Change From Baseline**	**Value**	**Change From Baseline**
	Hct (%)				
Baseline	Mean (SD)	29.6 (7.3)		28.2 (6.7)	
	N	29		34	
2 Weeks After Final Ferrlecit® Infusion	Mean (SD)	31.9 (7.1)	2.3 (4.1)	30.9 (6.8)	2.7 (3.8)
	N	29	29	34	34
	P-Value *	0.0058		0.0001	
	P-Value **	>0.05			
	TSAT (%)				
Baseline	Mean (SD)	18.5 (10.3)		16.0 (10.5)	
	N	28		34	
2 Weeks After Final	Mean (SD)	26.1 (14.0)	7.9 (13.9)	26.5 (16.1)	10.5 (13.5)

Ferrlecit® Infusion	N	29	28	34	34
	P-Value *	0.0014		<0.0001	
	P-Value **	>0.05			
	Serum Ferritin (ng/ml)				
Baseline	Mean (SD)	99.8 (133.6)		183.1 (262.6)	
	N	29		34	
2 Weeks After Final Ferrlecit® Infusion	Mean (SD)	284.7 (327.5)	184.8 (260.7)	490.3 (321.6)	307.2 (184.0)
	N	29		32	
	P-Value *	<0.0001		<0.0001	
	P-Value **	<0.0001			
	CHr (pg)				
Baseline	Mean (SD)	31.1 (3.1)		30.9 (2.8)	
	n	28		31	
2 Weeks After Final Ferrlecit® Infusion	Mean (SD)	32.6 (2.4)	1.3 (2.1)	32.1 (2.2)	1.2 (2.7)
	n	27	26	32	29
	P-Value *	0.0009		0.0051	
	P-Value **	>0.05			
	HCRBC (%)				
Baseline	Mean (SD)	9.2 (10.5)		7.5 (10.3)	
	n	28		31	
2 Weeks After Final Ferrlecit® Infusion	Mean (SD)	10.1 (13.3)	1.6 (9.4)	7.4 (9.3)	-1.2 (8.9)
	n	27	26	31	29
	P-Value *	0.8790		0.9646	
	P-Value **	>0.05			

*P-value calculations based on signed rank test by Dr. Milton C. Fan, Ph.D.
**P-value calculations between dose groups based on signed rank test by Dr. Milton C. Fan, Ph.D.
Reviewer's table

Drug-Drug and Drug-Disease Interactions

No formal drug-drug interaction or drug-disease analyses were conducted for the study. No significant drug- disease interactions were identified based on changes in concomitant medication use for concurrent disease states or from review of adverse events.

D. Efficacy Conclusions

One pediatric study (FR01006) was submitted to support the indication of treatment of iron deficiency anemia in pediatric patients 6-15 years of age undergoing chronic hemodialysis who are receiving supplemental epoetin therapy.

Study FR01006 was a multicenter, randomized, double-blind, parallel groups, dose-response study of Ferrlecit in pediatric patients who underwent chronic hemodialysis and who were receiving supplemental epoetin therapy. Two doses of Ferrlecit (1.5 mg/kg and 3.0 mg/kg of elemental iron) IV infusion were studied and were administered during eight consecutive hemodialysis sessions over an approximately 22 day period. Patients 2 to 15 years of age were eligible for the study. Patients with TSAT<20% and/or serum ferritin <100 ng/mL at baseline and receiving a stable EPO dosing regimen were enrolled in the study. The mean hemoglobin at baseline was 9.4 g/dL in study patients. The primary efficacy endpoint was the change in hemoglobin from baseline to two weeks following the last Ferrlecit administration.

A total of 88 patients were screened, 67 were enrolled and randomized at 21 sites from 5 countries. A total of 66 patients received study drug (32 in the 1.5 mg/kg group and 34 in the 3.0 mg/kg group) and 57 (85%) patients (25 in the 1.5 mg/kg group and 32 in the 3.0 mg/kg group) were evaluated for primary efficacy endpoint. Among the 66 patients who were treated in the study, patients ranged in age from 6 to 15 years (mean age of 12 years) and no children were under 6 years of age due to scarcity of patients in this age range. There were 38 (58%) patients with age 6-12 years and 28 (42%) patients with age 12-15 years. There were similar numbers of male (34, 52%) and female (32, 48%) patients. Majority of patients were Caucasian (Caucasian 71%, Asian 18%, Hispanic 6%, Black 2% and others 3%).

The primary efficacy results showed that the mean increase from baseline in hemoglobin at 2 weeks after the last Ferrlecit administration was 0.8 g/dL in the 1.5 mg/kg group and 0.9g/dL in the 3.0 mg/kg group based on completer patient population (57 patients). The hemoglobin values at 2 weeks after the last Ferrlecit administration were significantly increased in both 1.5 mg/kg and 3.0 mg/kg dosing groups as compared to baseline ($p=0.0033$ and <0.0001, respectively). The mean increase in hemoglobin was maintained at 4 weeks after the treatment in both dosing groups (0.9 g/dL in the 1.5 mg/kg group and 1.0g/dL in the 3.0 mg/kg group). There was no significant difference in mean changes from baseline in hemoglobin at 2 weeks after treatment between the two dosing groups ($p=0.75$). There were similar results based on all treated patient population (66 patients).

Results of the secondary efficacy analyses were consistent with those of the primary efficacy analysis. The response rates (increase in hemoglobin $\geq$1 g/dL) at 2 weeks after treatment were similar between the two dosing groups (40% in the 1.5 mg/kg group and 50% in the 3.0 mg/kg group, $p=0.45$). Hematocrit increased 2.6% at 2 weeks after treatment from baseline in the 1.5 mg/kg group [$p=0.0031$] and 3.0% in the 3.0 mg/kg group [$p<0.0001$]. There were significant increases from baseline in TSAT (5.5% in the 1.5 mg/kg group [$p<0.01$] and 10.5% in the 3.0 mg/kg group [$p<0.0001$]), serum ferritin (192 ng/mL in the 1.5 mg/kg group [$p<0.0001$]and 314 ng/mL in the 3.0 mg/kg group [$p<0.0001$]) and CHr (1.3 pg in the 1.5 mg/kg group [$p<0.01$] and 1.2 pg in the 3.0 mg/kg group [$p<0.05$]) at 2 weeks after treatment in both dosing groups. HCRBC was not changed at 2 weeks after treatment from baseline in either dosing group. There was no statistically significant difference for any secondary endpoint between the two dosing groups ($p>0.05$). The results for the secondary efficacy endpoints based on all treated population were similar to those for the completer patient population.

In conclusion, Study FR01006 showed significant increases in hemoglobin at 2 weeks after treatment from baseline in both dosing groups and the effect was maintained at 4 weeks after treatment. There was no significant difference in efficacy between the 1.5 mg/kg and 3.0 mg/kg Ferrlecit dosing regimens.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Study FR01006 showed the percentage of patients experiencing adverse events (about 80% of patients) and serious adverse events (about 15% of patients) was similar between the two dosing groups. The most common adverse events were hypotension (35%), headache (24%), hypertension (23%), tachycardia (17%), vomiting (11%), fever (9%), nausea (9%), abdominal pain (9%), pharyngitis (9%), diarrhea (8%), infection (8%), rhinitis (6%), and thrombosis (6%). More patients in the higher dosing (3.0 mg/kg) group experienced hypotension, tachycardia, fever, headache, abdominal pain, nausea, pharyngitis, and rhinitis than patients in the lower dosing (1.5 mg/kg) group. These safety results were based on pediatric patients 6 to 15 years of age. No safety data were available in pediatric patients younger than 6 years of age.

B. Description of Patient Exposure

Extent of Exposure

A total of 66 patients were exposed to Ferrlecit in the trial. Among the 66 patients, 60 (91%) patients received all eight infusions (28 in the 1.5 mg/kg group and 32 in the 3.0 mg/kg group), 3 (4.5%) patients received 7 infusions (2 in the 1.5 mg/kg group and 1 in the 3.0 mg/kg group), and 1 (1.5%) patient each received 5 (in the 3.0 mg/kg group) , 2 (in the 1.5 mg/kg group), and 1 (in the 1.5 mg/kg group) infusion, respectively (see table below).

Extent of exposure

Number of Infusions	1.5 mg/kg Ferrlecit N = 32		3.0 mg/kg Ferrlecit N = 34		Overall N = 66	
	n	%	n	%	n	%
1 infusion	1	3.1%	0	0.0%	1	1.5%
2 infusions	1	3.1%	0	0.0%	1	1.5%
3 infusions	0	0.0%	0	0.0%	0	0.0%
4 infusions	0	0.0%	0	0.0%	0	0.0%
5 infusions	0	0.0%	1	2.9%	1	1.5%
6 infusions	0	0.0%	0	0.0%	0	0.0%
7 infusions	2	6.3%	1	2.9%	3	4.5%
8 infusions	28	87.5%	32	94.1%	60	90.9%

Sponsor's table in NDA/SE5-006 submission FR01006 study report Table 12.1-1.

For the completer population, the mean (± SD) cumulative Ferrlecit doses administered to patients in the 1.5 mg/ kg and 3.0 mg/ kg treatment groups were 397 ±167 and 715 ± 201 mg, respectively. A total of eight patients were administered the maximum dose of 125 mg at each HD session (1.0 g total over the duration of the study) which included 2 patients in the 1.5 mg/kg treatment group and 6 patients in the 3.0 mg/ kg treatment group.

C. Methods and Specific Findings of Safety Review

Adverse Events

A total of 261 AEs were reported by 54 (81.8%) patients in the study. The number of patients reporting AEs was similar between the 1.5 mg/ kg (26 patients, 81.3%, 110 AEs) and the 3.0 mg/ kg (28 patients, 82.4%, 151 AEs) treatment groups.

An overall summary of the frequency of AEs is presented is the table below.

Overall summary of adverse events

Characteristic	1.5 mg/kg Ferrlecit N = 32		3.0 mg/kg Ferrlecit N = 34		Overall N = 66	
	n	%	n	%	n	%
Patients with at least one AE	26	81.3	28	82.4	54	81.8
Total number of AEs	110	--	151	--	261	--
Non-Treatment-related AEs[1]						
Patients with AEs	26	81.3	28	82.4	54	81.8
Number of AEs	107	--	150	--	257	--
Treatment-related AEs[1]						
Number. of patients with AEs	1	3.1	1	2.9	2	3.0
Number of AEs	3	--	1	--	4	--
Serious AEs						
Number of patients with AEs	5	15.6	5	14.7	10	15.2
Number of AEs	6	--	6	--	12	--
Discontinuations due to AEs	1	3.1	0	0.0	1	1.5
Number of patients discontinued with treatment-related AEs[1]	0	0.0	0	0.0	0	0.0
Number of patients discontinued with non-treatment-related AEs	1	3.1	0	0.0	1	1.5

[1] Treatment-related AEs are those determined by the investigator to be poss bly, probably, or definitely related to study drug.
Sponsor's table in NDA/SE5-006 submission FR01006 study report Table 12.2-1.

The most common AEs occurring in ≥ 5%, regardless of treatment group, were: hypotension (35%), headache (24%), hypertension (23%), tachycardia (17%), vomiting (11%), fever (9%), nausea (9%), abdominal pain (9%), pharyngitis (9%), diarrhea (8%), infection (8%), rhinitis (6%), and thrombosis (6%).

All treatment-emergent AEs by dosing group are listed in the table below.

Incidence and frequency of all treatment-emergent adverse events

Body System Costart Code	1.5 mg/kg Ferrlecit N = 32		3.0 mg/kg Ferrlecit N = 34		Overall N = 66	
	Patients	Events	Patients	Events	Patients	Events
	n (%)	n	n (%)	n	n (%)	n
Overall	26 (81.3)	110	28 (82.4)	151	54 (81.8)	261
Body as a Whole	10 (31.3)	28	17 (50.0)	41	27 (40.9)	69
asthenia	1 (3.1)	1	1 (2.9)	2	2 (3.0)	3
chills	0 (0.0)	0	1 (2.9)	1	1 (1.5)	1
edema face	1 (3.1)	1	0 (0.0)	0	1 (1.5)	1
fever	1 (3.1)	1	5 (14.7)	5	6 (9.1)	6

headache	6 (18.8)	15	10 (29.4)	20	16 (24.2)	35
hypertrophy	0 (0.0)	0	1 (2.9)	1	1 (1.5)	1
infection	3 (9.4)	6	2 (5.9)	2	5 (7.6)	8
pain	0 (0.0)	0	2 (5.9)	2	2 (3.0)	2
pain abdomen	1 (3.1)	2	5 (14.7)	7	6 (9.1)	9
pain back	1 (3.1)	1	0 (0.0)	0	1 (1.5)	1
pain chest	1 (3.1)	1	0 (0.0)	0	1 (1.5)	1
pain knee	0 (0.0)	0	1 (2.9)	1	1 (1.5)	1
Cardiovascular	20 (62.5)	45	21 (61.8)	75	41 (62.1)	120
hemorrhage	1 (3.1)	1	1 (2.9)	1	2 (3.0)	2
hypertension	7 (21.9)	15	8 (23.5)	20	15 (22.7)	35
hypotension	9 (28.1)	14	14 (41.2)	38	23 (34.8)	52
tachycardia	4 (12.5)	12	7 (20.6)	13	11 (16.7)	25
thrombosis	2 (6.3)	3	2 (5.9)	2	4 (6.1)	5
vascular disease peripheral	0 (0.0)	0	1 (2.9)	1	1 (1.5)	1
Digestive	4 (12.5)	10	10 (29.4)	26	14 (21.2)	25
constipation	0 (0.0)	0	1 (2.9)	1	1 (1.5)	1
diarrhea	3 (9.4)	4	2 (5.9)	2	5 (7.6)	6
dyspepsia	0 (0.0)	0	1 (2.9)	1	1 (1.5)	1
gastritis	0 (0.0)	0	1 (2.9)	1	1 (1.5)	1
nausea	2 (6.3)	2	4 (11.8)	4	6 (9.1)	6
vomit	3 (9.4)	4	4 (11.8)	7	7 (10.6)	11
Hemic and Lymphatic	1 (3.1)	2	2 (5.9)	3	3 (4.5)	5
anemia	0 (0.0)	0	1 (2.9)	1	1 (1.5)	1
eosinophilia	0 (0.0)	0	1 (2.9)	2	1 (1.5)	2
leukocytosis	1 (3.1)	1	0 (0.0)	0	1 (1.5)	1
lymphocytosis	1 (3.1)	1	0 (0.0)	0	1 (1.5)	1
Metabolic and Nutritional Disorders	3 (9.4)	3	3 (8.8)	4	6 (9.1)	7
edema	1 (3.1)	1	0 (0.0)	0	1 (1.5)	1
edema peripheral	0 (0.0)	0	1 (2.9)	2	1 (1.5)	2
hyperglycemia	0 (0.0)	0	1 (2.9)	1	1 (1.5)	1
hyperkalemia	2 (6.3)	2	0 (0.0)	0	2 (3.0)	2
water intoxication	0 (0.0)	0	1 (2.9)	1	1 (1.5)	1
Nervous	3 (9.4)	5	2 (5.9)	2	5 (7.6)	7
Costart Code	n (%)	n	n (%)	n	n (%)	n
convulsions	0 (0.0)	0	1 (2.9)	1	1 (1.5)	1
dizziness	2 (6.3)	4	1 (2.9)	1	3 (4.5)	5
neuralgia	1 (3.1)	1	0 (0.0)	0	1 (1.5)	1
Respiratory	5 (15.6)	6	8 (23.5)	8	13 (19.7)	14
bronchitis	0 (0.0)	0	1 (2.9)	1	1 (1.5)	1
pharyngitis	2 (6.3)	2	4 (11.8)	4	6 (9.1)	6
rhinitis	1 (3.1)	2	3 (8.8)	3	4 (6.1)	5
sinusitis	1 (3.1)	1	0 (0.0)	0	1 (1.5)	1
voice alteration	1 (3.1)	1	0 (0.0)	0	1 (1.5)	1
Skin	3 (9.4)	4	1 (2.9)	1	4 (6.1)	5
pruritis	2 (6.3)	2	0 (0.0)	0	2 (3.0)	2
rash	1 (3.1)	1	1 (2.9)	1	2 (3.0)	2
rash vesiculobullbous	1 (3.1)	1	0 (0.0)	0	1 (1.5)	1
Special Senses	1 (3.1)	3	0 (0.0)	0	1 (1.5)	3
blepharitis	1 (3.1)	1	0 (0.0)	0	1 (1.5)	1
conjunctivitis	1 (3.1)	1	0 (0.0)	0	1 (1.5)	1
pain eye	1 (3.1)	1	0 (0.0)	0	1 (1.5)	1
Urogenital	4 (12.5)	4	1 (2.9)	1	5 (7.6)	5
cystitis	0 (0.0)	0	1 (2.9)	1	1 (1.5)	1
kidney failure	1 (3.1)	1	0 (0.0)	0	1 (1.5)	1
menorrhagia	1 (3.1)	1	0 (0.0)	0	1 (1.5)	1
urinary frequency	1 (3.1)	1	0 (0.0)	0	1 (1.5)	1

urinary tract disease	1 (3.1)	1	0 (0.0)	0	1 (1.5)	1

Sponsor's table in NDA/SE5-006 submission FR01006 study report Table 12.2-2.

Reviewer's comments: Above table shows that more patients in the higher dosing (3.0 mg/kg) group thanpatients in the lower dosing (1.5 mg/kg) group experienced hypotension (41% vs. 28%), tachycardia(21% vs. 13%), fever (15% vs. 3%), headache (29% vs. 19%), abdominal pain (15% vs. 3%), nausea (12% vs. 6%), vomiting (12% vs. 9%), pharyngitis (12% vs. 6%), and rhinitis(9% vs. 3%). These suggest that these adverse events are dose-related to Ferrlecit administration.

Treatment-related adverse events

During the study, 4 adverse events were reported which the investigator considered to be related to study medication. These four treatment-related AEs occurred in two patients: nausea, vomiting, and diarrhea in one patient in the 1.5 mg/kg group, and anemia in one patient in the 3.0 mg/kg group. The following table listed treatment-related adverse events.

Incidence and frequency of all treatment- related adverse events by treatment

Body System Costart Code	**1.5 mg/kg Ferrlecit N = 32**		**3.0 mg/kg Ferrlecit N = 34**		**Overall N = 66**	
	Patients	**Events**	**Patients**	**Events**	**Patients**	**Events**
	n (%)	**(n)**	**n (%)**	**(n)**	**n (%)**	**(n)**
Overall	1 (3.1)	3	1 (2.9)	1	2 (3.0)	4
Digestive	1 (3.1)	3	0 (0.0)	0	1 (1.5)	3
Diarrhea	1 (3.1)	1	0 (0.0)	0	1 (1.5)	1
Nausea	1 (3.1)	1	0 (0.0)	0	1 (1.5)	1
Vomiting	1 (3.1)	1	0 (0.0)	0	1 (1.5)	1
Hemic and Lymphatic	0 (0.0)	0	1 (2.9)	1	1 (1.5)	1
Anemia	0 (0.0)	0	1 (2.9)	1	1 (1.5)	1

Sponsor's table in NDA/SE5-006 submission FR01006 study report Table 12.2-3.

Of the four treatment-related adverse events recorded during the study, one (anemia) was considered to be severe in nature by investigator.

Deaths

No deaths occurred during the study.

Other Serious Adverse Events

Ten patients (5 patients in each dosing group) experienced 12 serious AEs (6 events in each dosing group). These SAEs are listed in the following table.

Frequency of serious adverse events by dosing group

Body System	1.5 mg/kg Ferrlecit N = 32		3.0 mg/kg Ferrlecit N = 34	
	Patients	Events	Patients	Events
	n (%)	n	n (%)	n
Overall	5 (15.6)	6	5 (14.7)	6
Body as a Whole				
Hemodialysis catheter infection	1 (3.1)	1	0 (0.0)	0
Infection	1 (3.1)	1	0 (0.0)	0
Cardiovascular				
Worsening of hypertension	1 (3.1)	1	1 (2.9)	1
Leaking AV graft	0 (0.0)	0	1 (2.9)	1
Worsening thrombosis resulting in malfunctioning dialysis catheter	1 (3.1)	1	0 (0.0)	0
A-V fistula thrombosis	1 (3.1)	1	1 (2.9)	1
Metabolic and Nutritional disorder				
Overhydration	0 (0.0)	0	1 (2.9)	1
Hemic and lymphatic				
Worsening of anemia	0 (0.0)	0	1 (2.9)	1
Urogenital				
Progression of ESRD	1 (3.1)	1	0 (0.0)	0
Nervous				
Epilepsy	0 (0.0)	0	1 (2.9)	1

Reviewer's table based on NDA submission in FR01006 study report listing 14.3.2.1

One serious adverse event (worsening of anemia) occurred in the 3.0 mg/kg group was considered by the investigator to be related to study drug. An excluded medication (packed red blood cells) was administered to the patient during this event. Administration of this excluded medication resulted in the patient being withdrawn from further study participation.

Other Significant Adverse Events

Discontinuation

One patient in the 1.5 mg/kg group discontinued treatment due to progression of renal failure requiring kidney transplant. No patients were discontinued due to an adverse event related to study drug treatment in the study.

Non-anaphylactic allergic reaction/anaphylactic reaction

No allergic reaction or anaphylactic reaction to Ferrlecit administration was reported in the study.

Hypotension

There were 52 reported instances of hypotension occurring in 23 patients (34.8%); 14 events occurring in 9 patients (28.1%) in the 1.5 mg/ kg treatment group and 38 events occurring in 14 patients (41.2%) in the 3.0 mg/ kg treatment group.

These instances of hypotension were not considered significant by the investigators for this patient population and were considered by the investigators to be related to the ultrafiltration procedure itself and not to Ferrlecit administration.

Clinical Laboratory Evaluation

No adverse trends were observed in the clinical laboratory parameters monitored during the study. No reported instances of laboratory values outside of the normal range were considered by the investigator to be related to study drug.

No adverse trends or changes were observed for laboratory tests including hematological or serum chemistry parameters.

Because of the advanced degree of morbidity and the nature of ESRD, no hematology and serum chemistry shift analyses were conducted.

Laboratory values outside of the normal range and considered clinically significant by the investigator were to be reported as AEs. The laboratory values noted to be outside of the normal ranges were characteristic for this patient population. There were no AE reports of abnormal values that were related to Ferrlecit administration.

Vital Signs

No adverse trends were identified in the mean and median values for systolic and diastolic blood pressure, pulse, respiration or body temperature between the treatment groups and within treatment groups across visits. Individual changes in vital signs occurred intermittently throughout the study. No AEs related to changes in vital signs were reported. Investigator evaluations of hypotensive events indicated that all such occurrences were related either to the patient's history of hypotension and/ or to the HD procedure itself and not to Ferrlecit administration.

Physical Examination

A physical examination was conducted during the first screening visit. The physical condition of the patients at that time was found to be representative of someone with ESRD who was undergoing regular HD 2 to 4 times per week. A physical examination was not conducted at the end of the patients' study participation. A change in physical examination findings could therefore not be assessed.

Other Safety Information

Study FR02001

A study investigating the use of Ferrlecit in the treatment of iron-deficient anemia in pediatric End Stage Renal Disease patients undergoing chronic hemodialysis is presently in progress

(Watson study FR02001). As of 29 January, 2004, 42 patients had been screened. Of these 42 potential participants, 23 were enrolled into the study and received drug, and 13 patients have completed the study with 4 more currently active in dosing.

The study is ongoing and no safety or efficacy results are presently available. Seven (7) serious adverse event reports have been submitted to the sponsor, during the course of the study. All 7 SAEs were considered by the investigators to not be related to Ferrlecit. The sponsor did not provide these adverse events in detail.

Spontaneous Adverse Experience Reporting

The source of information includes the sponsor's drug safety database (b) (4) reports provided by Aventis (holder of European marketing rights for Ferrlecit), and MedWatch review. All three sources were reviewed for presence of cases involving Ferrlecit in pediatric patients by the sponsor. A formal integration of these data with the results of the clinical study has not been performed; however, the post-marketing data are described in relation to the results of the clinical study.

A total of 7 post-marketing adverse events for Ferrlecit in pediatric patients (age range 17 months to 16 years) have been reported worldwide. No deaths were reported. Two reports were for allergic reactions, one of which was classified as anaphylactoid in nature. These allergic events had either a possible or a conditional relationship to Ferrlecit. Other post-marketing adverse events included symptoms that have been previously reported with Ferrlecit, such as headache, urticaria, pruritis, rash, dyspnea, facial edema, flushing, tachycardia, abdominal pain, vasodilatation, nausea, diarrhea, vomiting, pallor, fever, and gastritis.

The reported adverse events were associated with doses that ranged from 0.5 mg (17-month-old patient) to 250 mg (9-and l3- year- old patients). The doses received are summarized by age and gender as follows:

Case Identification	Age	Gender	Dose	Event	Outcome
20011202EU	17 months	Male	0.5 mg	Allergic reaction- - hypertonia - vomiting - pallor - fever	Recovered
200110292GDDC	9 years	Male	250 mg	Urticaria	Recovered
200313258EU	10 years	Male	62.5 mg	Dyspnea Face Oedema Rash Tachycardia	Recovered
DE01-03377	12 years	Female	NR	Anaphylactoid reaction	Recovered
2001-00172	13 years	Female	125 mg + 62.5 mg + 62.5 mg	Headache	Recovered
200023350GDDC	16 years	Male	25/50 mg	Pruritis	Recovered
200210007GDDC	16 years	Female	125 mg	Tachycardia Hypertension Vasodilatation Abdominal Pain Diarrhea Nausea	Recovered

NR, not reported

Sponsor's table in NDA/SE5-006 submission Vol. 22, p 178.

One patient (Case 200ll0292GDDC) received a 250 mg dose and a second patient (Case 2001-00172) appears to have received three doses on the same day for a total dose of 250 mg.

D. Adequacy of Safety Testing

One study was conducted in pediatric patients with iron deficiency anemia undergoing chronic hemodialysis who were receiving supplemental epoetin therapy. A total of 67 patients were enrolled at 21 centers in five countries. Enrolled patients were from 6 to 15 years of age and patients younger than 6 years of age were not enrolled in the study because of the limited availability of patients in this age group. A total of 66 patients with age of 6 to 15 years were treated by Ferrlecit. Among the 66 patients, 60 (91%) patients received all eight infusions (28 in the 1.5 mg/kg group and 32 in the 3.0 mg/kg group). The safety testing of Ferrlecit in pediatric patients 6 to 15 years of age appears adequate.

E. Summary of Critical Safety Findings and Limitations of Data

One study (Study FR01006) was conducted in pediatric patients with iron deficiency anemia who were undergoing chronic hemodialysis and who were receiving supplemental epoetin therapy. A total of 67 patients 6 to 15 years of age were enrolled and 66 patients were treated in the study. Among the 66 patients, 60 (91%) patients received all eight infusions (28 in the 1.5 mg/kg group and 32 in the 3.0 mg/kg group), 3 (4.5%) patients received 7 infusions (2 in the 1.5

mg/kg group and 1 in the 3.0 mg/kg group), and 1 (1.5%) patient each received 5 (in the 3.0 mg/kg group) , 2 (in the 1.5 mg/kg group), and 1 (in the 1.5 mg/kg group) infusion, respectively.

In the study, 81.8% (54/66) of patients reported adverse events. The number of patients reporting adverse events (AEs) was similar between the 1.5 mg/kg treatment group (26 patients, 81.3%, 110 AEs) and the 3.0 mg/ kg treatment group (28 patients, 82.4%, 151 AEs). The overall most common AEs occurring in ≥5%, regardless of treatment group, were: hypotension (35%), headache (24%), hypertension (23%), tachycardia (17%), vomiting (11%), fever (9%), nausea (9%), abdominal pain (9%), pharyngitis (9%), diarrhea (8%), infection (8%), rhinitis (6%), and thrombosis (6%). The study showed that more patients in the higher dosing (3.0 mg/kg) group than in the lower dose group (1.5 mg/kg) experienced the following adverse events: hypotension (41% vs. 28%), tachycardia (21% vs. 13%), fever (15% vs. 3%), headache (29% vs. 19%), abdominal pain (15% vs. 3%), nausea (12% vs. 6%), vomiting (12% vs. 9%), pharyngitis (12% vs. 6%), and rhinitis (9% vs. 3%). Only 4 reported adverse events were considered to be related to study treatment by the investigator (nausea, vomiting, and diarrhea in one patient in the 1.5 mg/kg group, and anemia in one patient in the 3.0 mg/kg group).

There were 52 reported instances of hypotension occurring in 23 patients (34.8%); 14 events occurred in 9 patients (28.1%) in the 1.5 mg/kg treatment group and 38 events occurred in 14 patients (41.2%) in the 3.0 mg/kg treatment group. These instances of hypotension were not considered significant by the investigators for this patient population and were considered by the investigators to be related to the ultrafiltration procedure itself and not to Ferrlecit administration.

No deaths occurred during the study. A total of 12 serious adverse events (SAEs) were reported in 10 patients and the frequency of the reported SAEs was similar between the two dosing groups (5 patients reported 6 SAEs in each dosing groups). The SAEs included hemodialysis catheter related (infection [1], thrombosis [3] and leaking [1]), worsening of hypertension (2), infection (1), overhydration (1), worsening of anemia (1), progression of ESRD (1), and epilepsy (1). Only worsening of anemia was considered by the investigator to be related to the study treatment.

One patient in the 1.5 mg/kg group discontinued treatment due to progression of renal failure requiring kidney transplant. No patients were discontinued due to an adverse event related to study drug treatment in the study. No allergic reaction or anaphylactic reaction to Ferrlecit administration was reported in study.

In conclusion, Study FR01006 showed the frequency of adverse events (about 80%) and serious adverse events (about 15%) was similar between the two dosing groups. The most common adverse events were hypotension (35%), headache (24%), hypertension (23%), tachycardia (17%), vomiting (11%), fever (9%), nausea (9%), abdominal pain (9%), pharyngitis (9%), diarrhea (8%), infection (8%), rhinitis (6%), and thrombosis (6%). More patients in the higher dosing (3.0 mg/kg) group experienced hypotension, tachycardia, fever, headache, abdominal pain, nausea, pharyngitis, and rhinitis than patients in the lower dosing (1.5 mg/kg) group.

These safety results were based on pediatric patients 6 to 15 years of age. No safety data were available in pediatric patients younger than 6 years of age.

VIII. Dosing, Regimen, and Administration Issues

Two doses of Ferrlecit (1.5 mg/kg and 3.0 mg/kg) were studied in the trial. Both Ferrlecit dosing regimens showed significant increases from baseline in hemoglobin at 2 weeks after treatment (0.8 g/dL and 0.9 g/dL, respectively). No significant dose-response was seen for change in hemoglobin. The secondary efficacy analysis showed a statistically significant difference in the increase in serum ferritin from baseline to two weeks after the treatment between the two dosing groups (192 ng/mL in the 1.5 mg/kg group and 314 ng/mL in the 3.0 mg/kg group, p=0.0003). This suggests a dose-response relationship between the Ferrlecit dose and the increase in serum ferritin level. No dose-response relationship was observed for other secondary efficacy endpoints including Hct, CHr and HCRBC.

The safety results showed that more patients in the higher dosing (3.0 mg/kg) group experienced hypotension, tachycardia, fever, headache, abdominal pain, nausea, pharyngitis, and rhinitis than those in the lower dosing (1.5 mg/kg) group. This suggests these adverse events are dose-related.

To minimize the risk of adverse reactions with Ferrlecit, the 1.5 mg/kg dosing regimen should be recommended for pediatric patients 6 to 15 years of age in the labeling.

No patients younger than 6 years of age were included in the trial. Therefore, no dose recommendation can be made for patients younger than 6 years of age.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

There were 34 males and 32 females who received Ferrlecit infusion in Study FR01006.

Hemoglobin

The following table shows the change in hemoglobin by gender. There was no significant difference in increase in hemoglobin at 2 weeks from baseline between males and females. No statistically significant difference was seen between the two treatment groups for either males or females.

Change in Hemoglobin by gender

Time of Evaluation	Statistic	1.5 mg/kg Ferrlecit® N = 25		3.0 mg/kg Ferrlecit® N = 32	
		Value	Change From Baseline	Value	Change From Baseline
Baseline					
Female	Mean (SD	10.1 (2.1)		9.2 (2.2)	
	n	14		15	
Male	Mean (SD)	9.2 (2.2)		9.6 (2.4)	
	n	11		17	
2 Weeks After Final Ferrlecit® Infusion					
Female	Mean (SD)	10.8 (2.3)	0.7 (1.5)	10.3 (2.1)	12 (1.3)
	n	14	14	15	15
	P-Value *		0.2103		0.0038
	P-Value **		0.1109		
Male	Mean (SD)	10.2 (2.1)	1.0 (1.0)	10.4 (2.2)	0.8 (1.0)
	n	11	11	17	17
	P-Value *		0.0073		0.0044
	P-Value **		0.4862		
4 Weeks After Final Ferrlecit® Infusion					
Female	Mean (SD)	11.2 (2.1)	0.8 (1.7)	10.5 (2.4)	1.3 (1.8)
	n	13	13	15	15
Male	Mean (SD)	10.1 (2.3)	0.9 (1.8)	10.4 (2.3)	0.8 (1.3)
	n	11	11	17	17

*P-value calculations based on a paired t-test with the null hypothesis that the change from baseline equals 0.
** P-value calculations based on a two-sample t-test with the null hypothesis of no difference between dose groups.
Sponsor's table in NDA/SE5-006 submission FR01006 study report Table 11.4-6.

Response
There was no statistically significant difference in proportion of responders (defined as an increase from baseline in hemoglobin of 1.0 g/dL or more at 2 weeks after treatment) between males and females in either 1.5 mg/kg or 3.0 mg/kg treatment group.

Hct, TSAT, Serum Ferritin, CHr, and HCRBC
Statistically significant increases in mean serum ferritin occurred in both the female and male populations in the 1.5 mg/ kg treatment group ($p = 0.0001$ and 0.0010, respectively) and in the 3.0 mg/ kg treatment group ($p = 0.0001$ and < 0.0001, respectively). There was significant difference in the mean change from baseline in ferritin between treatment groups for both the female ($p = 0.0471$) and male ($p = 0.0022$) populations.

There was no observed significant difference between males and females in change from baseline for Hct, TSAT, HCRBC, and CHr.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Age effect

There were 38 patients with age of 6 to12 years and 28 patients with age of 13 to 15 years in the study. No patient younger than 6 years of age was enrolled.

Hemoglobin

The following table shows the mean change from baseline in hemoglobin by age group.

The mean change from baseline in Hgb at 2 weeks after treatment was 1.0 g/dL for both treatment groups for patients with age of 6 to 12 years. For patients with age of 13 to 15 years, the mean changes from baseline in Hgb were 0.7 g/dL in the 1.5 mg/kg treatment group and 0.8 g/dL in the 3.0 mg/kg treatment group. There was no significant difference in the mean change from baseline in Hgb values between treatment groups in either age group. The increase in Hgb from baseline was not significantly different between age groups.

Hgb (g/dl) response by age group

Time of Evaluation	**Statistic**	**1.5 mg/kg Ferrlecit® N = 25**		**3.0 mg/kg Ferrlecit® N = 32**	
		Value	**Change From Baseline**	**Value**	**Change From Baseline**
Baseline					
6-12 years	Mean (SD)	9.5 (2.1)		8.9 (2.1)	
	n	12		21	
13-15 years	Mean (SD)	9.9 (2.3)		10.5 (2.4)	
	n	13		11	
2 Weeks After Final Ferrlecit® Infusion					
6-12 years	Mean (SD)	10.5 (2.5)	1.0 (1.6)	9.9 (2.1)	1.0 (1.0)
	n	12	12	21	21
	P-Value *		0.0480		0.0001
	P-Value **		0.9915		
13-15 years	Mean (SD)	10.6 (2.0)	0.7 (1.0)	11.3 (2.0)	0.8 (1.4)
	n	13	13	11	11
	P-Value *		0.0297		0.0849
	P-Value **	0.8140			
4 Weeks After Final Ferrlecit® Infusion					
6-12 years	Mean (SD)	10.2 (2.6)	0.8 (2.1)	10.0 (2.2)	1.2 (1.3)
	n	12	12	21	21
13-15 years	Mean (SD)	11.2 (1.8)	1.0 (1.2)	11.3 (2.5)	0.8 (2.0)
	n	12	12	11	11

* P-value calculations based on a paired t-test with the null hypothesis that the change from baseline equals 0.

** P-value calculations based on a two-sample t-test with the null hypothesis of no difference between dose groups.

Sponsor's table in NDA/SE5-006 submission FR01006 study report Table 11.4-5.

Response

There was no significant difference in response rate between treatment groups within each age group or between different age groups.

Hct, TSAT, Serum Ferritin, CHr, and HCRBC
Statistically significant improvements in mean serum ferritin changes occurred in both the 6 to 12 and the 13 to 15 year old populations in the 1.5 mg/ kg treatment group ($p = 0.0005$ and 0.0002, respectively) and in the 3.0 mg/ kg treatment group ($p < 0.0001$ and 0.0009, respectively). There was significant difference in the mean changes from baseline in ferritin between treatment groups in the 6 to 12 year old population ($p = 0.0023$), and a borderline significant between treatment groups in the 13 to 15 year old population ($p = 0.0637$).

There was no observed significant difference between age groups in change from baseline for Hct, TSAT, HCRBC, and CHr.

Race effect

There were 47 Caucasian, 12 Hispanic, 4 Black, 1 Asians, and 2 others enrolled in the trial. The sponsor did not perform analysis by race.

C. Evaluation of Pediatric Program

This submission includes the pediatric study report submitted in response to Written Request for Pediatric Studies.

D. Comments on Data Available or Needed in Other Populations

There are no comments regarding other populations at this time.

X. Conclusions and Recommendations

A. Conclusions

One multicenter, randomized, double-blind, dose response study was conducted in 67 pediatric patients 6 to 15 years of age undergoing chronic hemodialysis who were receiving epoetin supplemental therapy. The study showed a significant increase from baseline in hemoglobin at 2 weeks after treatment and a lower incidence of hypotension, tachycardia, fever, headache, abdominal pain, nausea, pharyngitis, and rhinitis with Ferrlecit 1.5 mg/kg dosing as compared to Ferrlecit 3.0 mg/kg dosing regimen.

Pediatric patients younger than 6 years of age were not studied in the clinical trial.

B. Recommendations

From a clinical perspective, Ferrlecit is approvable for the treatment of iron deficiency anemia in pediatric patients 6 to 15 years of age who are undergoing chronic hemodialysis and who are receiving supplemental epoetin therapy. The recommended dose regimen is 0.12 mL/kg (1.5 mg/kg of elemental iron) by intravenous infusion during eight consecutive hemodialysis sessions.

XI. Appendix

A. Labeling recommendations

Ferrlecit®
(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 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 first stage, each subject was randomized 1:1 to undiluted Ferrlecit® injection of either 125 mg/hr or 62.5 mg/0.5 hr (2.1 mg/min). Five days after the first stage, each subject was re-randomized 1:1 to undiluted Ferrlecit® injection of either 125 mg/7 min or 62.5 mg/4 min (>15.5 mg/min).

Peak drug levels (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 17.5 mg-h/L (62.5 mg) to 35.6 mg-h/L (125 mg). There was no significant variation by rate of administration. Approximately 80% of drug bound iron was delivered to transferrin as a mononuclear 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.

Pediatrics: Single dose intravenous pharmacokinetic analyses were performed on 48 iron-deficient pediatric hemodialysis patients. Twenty-two patients received 1.5 mg/kg Ferrlecit® and 26 patients received 3.0 mg/kg Ferrlecit® (maximum dose 125 mg). The mean C_{max}, $AUC_{0-\infty}$, and terminal elimination half-life values for the 22 patients who received a 1.5 mg/kg dose were 12.9 mg/L, 95.0 mg•hr/L, and 2.0 hours, respectively. The mean C_{max}, $AUC_{0-\infty}$, and terminal elimination half-life values for the 26 patients who received a 3.0 mg/kg dose were 22.8 mg/L, 170.9 mg•hr/L, and 2.5 hours, respectively.

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

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

CLINICAL STUDIES

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

Study A

Study A was a three-center, randomized, open-label study of the safety and efficacy of two doses of Ferrlecit® administered intravenously to iron-deficient hemodialysis patients. The study included both a dose-response 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® (sodium ferric gluconate complex in sucrose injection) group (50% female, 50% male; 74% white, 18% black, 5% Hispanic, 3% Asian; mean age 54 years, range 22-83 years), 44 patients in the high-dose Ferrlecit® group (50% female, 48% male, 2% unknown; 75% white, 11% black, 5% Hispanic, 7% other, 2% unknown; mean age 56 years, range 20-87 years), and 25 historical control patients (68% female, 32% male; 40% white, 32% black, 20% Hispanic, 4% Asian, 4% unknown; mean age 52 years, range 25-84 years).

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 (g/dL)	1.1*	0.3	0.4
Hematocrit (%)	3.6*	1.4	0.8
Transferrin Saturation (%)	8.5	2.8	6.1
Serum Ferritin (ng/mL)	199	132	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 (37% female, 63% male; 95% white, 5% Asian; mean age 56 years, range 22-84 years) and 25 in the historical control group (68% female, 32% male; 40% white, 32% black, 20% Hispanic, 4% Asian, 4% unknown; mean age 52 years, range 25-84 years).

Ferrlecit®-treated patients were considered to have completed the study per protocol if they received at least 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.

Study C

Study C was a multicenter, randomized, open-label study of the safety and efficacy of two Ferrlecit® dose regimens (1.5 mg/kg or 3.0 mg/kg of elemental iron) administered intravenously to 66 iron-deficient (transferrin saturation < 20% and/or serum ferritin < 100 ng/mL) pediatric hemodialysis patients, 6 to 15 years of age, inclusive who were receiving a stable erythropoietin dosing regimen.

Ferrlecit® at a dose of 1.5 mg/kg or 3.0 mg/kg (up to a maximum dose of 125 mg of elemental iron) in 25 mL 0.9% sodium chloride was infused intravenously over 1 hour during each hemodialysis session for eight sequential dialysis sessions. Thirty-two patients received the 1.5 mg/kg dosing regimen (47% male, 53% female; 66% Caucasian, 25% Hispanic, and 3% Black, Asian, or Other; mean age 12.3 years). Thirty-four patients received the 3.0 mg/kg dosing regimen (56% male, 44% female; 77% Caucasian, 12% Hispanic, and 9% Black, 3% Other; mean age 12.0 years).

The primary endpoint was the change in hemoglobin concentration from baseline to 2 weeks after last Ferrlecit® administration. Patients in both Ferrlecit® dose groups had statistically significant changes from baseline in hemoglobin concentrations (Table 3). There was no significant difference between the treatment groups. Statistically significant improvements in hematocrit, transferrin saturation, serum ferritin, and reticulocyte hemoglobin concentrations compared to baseline values were observed 2 weeks after the last Ferrlecit® infusion in both the 1.5 mg/kg and 3.0 mg/kg treatment groups (Table 3).

Table 3
Hemoglobin, Hematocrit, and Iron Status

Study C	Mean Change From Baseline to Two Weeks After Cessation of Therapy in Patients Completing Treatment	
	1.5 mg/kg Ferrlecit® (N = 25)	3.0 mg/kg Ferrlecit® (N = 32)
Hemoglobin (g/dL)	0.8 *	0.9 *
Hematocrit (%)	2.6 *	3.0 *
Transferrin Saturation (%)	5.5 *	10.5*
Serum Ferritin (ng/mL)	192 *	314 *
Reticulocyte Hemoglobin Content (pg)	1.3 *	1.2 *

* $p < 0.03$ verses the baseline values

The increased hemoglobin concentrations were maintained at 4 weeks after the last Ferrlecit® infusion in both the 1.5 mg/kg and the 3.0 mg/kg Ferrlecit® dose treatment groups.

INDICATIONS AND USAGE
Ferrlecit® (sodium ferric gluconate complex in sucrose injection) is indicated for treatment of iron deficiency anemia in adult patients and in pediatric patients age 6 years and older 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: Ferrlecit® was shown to be safe and effective in pediatric patients ages 6 to 15 years (refer to CLINICAL STUDIES section). Safety and effectiveness in pediatric patients below the age of 6 years 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®-naïve 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 1,097 patients who received Ferrlecit® in this study, there were 9 patients (0.8%) who had an adverse reaction that, in the view of the investigator, precluded further Ferrlecit® 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 1,034 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 incidences 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 22/1,097 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® (sodium ferric gluconate complex in sucrose injection) were reported in North American clinical trials when normalized against a National Institute of Health database on laboratory findings in 1,100 hemodialysis patients.

Most Frequent Adverse Reactions: In the single-dose, post-marketing safety study, 11% of patients 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.

Respiratory System: dyspnea (11%), coughing (6%), upper respiratory infections (6%), rhinitis, pneumonia.

Cardiovascular System: hypotension (29%), hypertension (13%), syncope (6%), tachycardia (5%), bradycardia, vasodilatation, angina pectoris, myocardial infarction, pulmonary edema.

Gastrointestinal System: nausea, vomiting and/or diarrhea (35%), anorexia, rectal disorder, dyspepsia, eructation, flatulence, gastrointestinal disorder, melena.

Musculoskeletal System: leg cramps (10%), myalgia, arthralgia.

Skin and 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.

Pediatric Patients: : In a clinical trial of 66 iron-deficient pediatric hemodialysis patients, 6 to 15 years of age, inclusive, who were receiving a stable erythropoietin dosing regimen, the most common adverse events occurring in ≥ 5%, regardless of treatment group, were: hypotension (35%), headache (24%), hypertension (23%), tachycardia (17%), vomiting (11%), fever (9%), nausea (9%), abdominal pain (9%), pharyngitis (9%), diarrhea (8%), infection (8%), rhinitis (6%), and thrombosis (6%). More patients in the higher dose group (3.0 mg/kg) than in the lower dose group (1.5 mg/kg) experienced the following adverse events: hypotension (41% vs. 28%), tachycardia (21% vs. 13%), fever (15% vs. 3%), headache (29% vs. 19%), abdominal pain (15% vs. 3%), nausea (12% vs. 6%), vomiting (12% vs. 9%), pharyngitis (12% vs. 6%), and rhinitis (9% vs. 3%).

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.

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

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

If diluted in saline, use immediately after dilution.

HOW SUPPLIED
NDC 52544-922-26

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.

Keep out of the reach of children.

Rx Only

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

/s/

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7/14/04 05:15:11 PM
MEDICAL OFFICER

Kathy Robie-Suh
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