Clinical Pharmacology and Biopharmaceutics Review

NDA: **20-955 / SE5-006**

Generic Name: Sodium Ferric Gluconate Complex in Sucrose Injection

Sponsor: Watson Laboratories, Inc.

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

Type of Submission: Efficacy Supplement for Pediatric Labeling

Proposed Indication: Treatment of iron Deficiency Anemia in Pediatric Patients Undergoing Chronic Hemodialysis and Receiving Supplemental Erythropoietin

Submission Date: 2/13/04

ORM Division: GI & Coagulation Drug Products

OCPB Division: DPE II

Team Leader: Suresh Doddapaneni, Ph.D.

Proposed Dosage Regimen: 1.5 mg/kg of elemental iron administered by I.V. infusion over 1 hour at eight sequential dialysis sessions

I. Executive Summary

Ferrlecit is a macromolecular complex with an apparent molecular weight of 350,000 ± 23,000 D. Ferrlecit is formed by chelation of gluconate molecules to ferric ions. It was first approved for marketing in the US on 2/18/99 for the treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental epoetin therapy.

Ferrlecit is currently not indicated for use in pediatrics as the safety and effectiveness of Ferrlecit in pediatrics have not yet been established. To obtain needed pediatric information on Ferrlecit, the Agency issued a formal Written Request for pediatric studies for Ferrlecit® Injection on 8/9/02 (see Appendix A).

Per Agency request in the PWR for Ferrlecit, the current submission consists of a single randomized, double-blind, parallel group PK and dose-response study (using two doses) in pediatric patients with iron deficiency undergoing chronic hemodialysis and are receiving supplemental erythropoietin therapy.

Based on the study finding of reduced clearance of Ferrlecit in pediatric patients relative to historical data in adults, a single dose of 1.5 mg/kg of Ferrlecit with a total dose of 125 mg per session should not be exceeded in pediatric patients with iron deficiency undergoing chronic hemodialysis that are receiving supplemental erythropoietin therapy. This is consistent with the sponsor's proposed recommendations for pediatric labeling.

The sponsor has adequately characterized the single dose PK of Ferrlecit in iron-deficient pediatric hemodialysis patients requiring repletion iron therapy.

A. Recommendations

From the view point of Office of Clinical Pharmacology and Biopharmaceutics, NDA 20-955-SE5-006 is **acceptable** provided that a satisfactory agreement is reached between the Agency and the sponsor with respect to proposed language in the Package Insert. See Appendix B for Agency proposed changes to the sponsor's proposed labeling.

B. Phase IV Commitments

None.

II. Table of Contents

III. Summary of CPB Findings

Per the issued PWR for Ferrlecit, the sponsor conducted a single, randomized, double-blind, multiple dose study to assess the effectiveness and single dose PK profiles for two Ferrlecit doses (1.5 and 3.0 mg/kg) in 66 pediatric patients (aged 6-16 years) with iron deficiency undergoing chronic hemodialysis that were receiving supplemental erythropoietin therapy.

While mean Cmax values in pediatric patients are comparable to those of historical healthy iron-deficient adults, mean AUC values are twice as high, indicating a reduced clearance in pediatric patients relative to healthy iron-deficient adults.

IV. Question-Based Review

A. General Attributes

Ferrlecit is a macromolecular complex with an apparent molecular weight of 350,000 ± 23,000 D. The complex is formed by chelation of gluconate molecules to ferric ions.

Ferrlecit was approved for marketing in the US on 2/18/99 for treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental epoetin therapy.

Each ampule of 5 ml Ferrlecit for I.V. injection contains 62.5 mg (12.5 mg/mL) of elemental iron as the sodium salt of a ferric ion carbohydrate complex in an alkaline aqueous solution with approximately 20% sucrose (w/v) in water for injection, pH 7.7-9.7. Each mL also contains 9 mg of benzyl alcohol as an inactive ingredient.

B. General Clinical Pharmacology

1. Do the findings of the PK study support the proposed dosage recommendations in pediatric patients aged 6-16 years?

Study FR01006 evaluated the comparative effectiveness and single dose PK profiles for two Ferrlecit doses in pediatric patients with iron deficiency undergoing chronic hemodialysis that were receiving supplemental erythropoietin therapy.

The study was a randomized, double-blind, multiple dose, parallel-group, multi-center study in pediatric hemodialysis (HD) patients (n = 66, age 12.1 ± 2.6 yrs, Wt 35.0 ± 16.6 kg). Patients determined to be iron-deficient[1] following suspension of their normal iron supplementation for 4 weeks (i.e., at Screening Visit 5), were randomized to a Ferrlecit dose of either 1.5 mg/kg (n = 22) or 3.0 mg/kg (n = 26), infused I.V. by syringe pump over 1 hour, not to exceed 125 mg per dose, during eight consecutive HD sessions over an approximate 22 day period. Blood samples were drawn for determination of Ferrlecit PK at 0 (pre-dose), 0.5, 1, 1.25, 1.5, 2, 3, 4, 6 and 48 hrs.

Table 1. Summary of the PK parameters following administration of 1.5 mg/kg and 3 mg/kg single doses of Ferrlecit to iron-deficient pediatric hemodialysis (HD) patients

Pharmacokinetic Parameter	1.5 mg/kg Ferrlecit® (n = 22)	3.0 mg/kg Ferrlecit® (n = 26)
C_{max} (mean ± SD μg/dL)	1287 ± 285	2283 ± 637
AUC_{0-48} (mean±SD μg•hr/dL)	9327 ± 4038	16,830 ± 6526
$AUC_{0-\infty}$ (mean ± SD μg•hr/dL)	9499 ± 4089	17,087 ± 6776
T_{max} (median hrs)	1.0	1.0
$t_{1/2}$ (median hrs)	2.0	2.1
K_{el} (mean ± SD hr-1)	0.43 ± 0.30	0.39 ± 0.27
Cl (mean ± SD L/hr)	0.69 ± 0.50	0.66 ± 0.52
V_d (mean ± SD L)	1.6 ± 0.6	1.9 ± 1.1

[1] Defined as having TSAT < 20% and/or serum ferritin < 100 ng/ml.

Mean serum iron concentrations (total iron and Ferrlecit®-bound iron) increase in a dose-dependent manner that is approximately proportional to the I.V. administered Ferrlecit dose (Table 1). The study findings also indicate that Cmax values in the pediatric population were comparable to those of adults with similar Ferrlecit doses (125 mg infused over 1 hour). However, mean AUC values were approximately two-fold higher while total systemic clearance was five-fold lower in the pediatric ESRD population relative to the adults. In addition, the volume of distribution (Vd) was around eight-fold lower in pediatric patients relative to adults (Table 2). It is noteworthy that the historical adult PK data is based on the findings of study FER9801, which evaluated the PK of Ferrlecit in healthy iron-deficient adults. This may account for the observed differences in the PK parameters of Ferrlecit between pediatric hemodialysis patients and healthy iron-deficient adults.

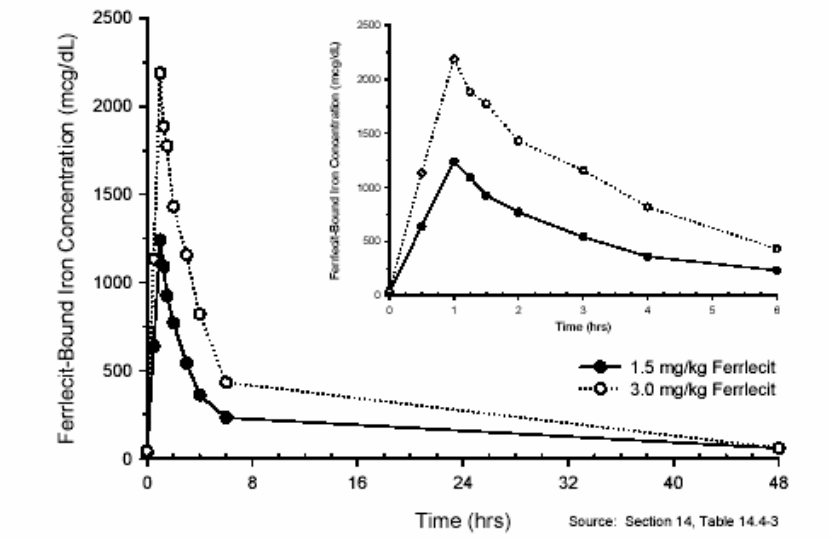

Fig. 1. Time course of Ferrlecit-bound iron concentrations following I.V. infusion of Ferrlecit (1.5 and 3.0 mg/kg).

Table 2. Summary of the mean pediatric and adult PK parameters

Pharmacokinetic Parameter	Pediatric Population N = 22	Adult Population N = 7
C_{max} (mean; µg/dL)	1287	1551
$AUC_{0-\infty}$ (mean; µg•hr/dL)	9499	3772
$t_{1/2}$ (median; hrs)	2.0	-- *
Cl (mean; L/hr)	0.69	3.58
V_d (mean; liters)	1.62	13.4

Overall, the study findings suggest that a single dose of 1.5 mg/kg of Ferrlecit with a total dose of 125 mg per session should not be exceeded in pediatric patients with iron deficiency undergoing chronic hemodialysis that are receiving supplemental erythropoietin therapy. This is consistent with the sponsor's recommended dosage in pediatric patients aged 6-16 years.

E. General Biopharmaceutics

None

F. Analytical Section

Ferrlecit-bound iron is calculated as the difference between the total (transferrin-bound plus Ferrlecit-bound) iron and transferrin-bound iron. Serum samples were assayed for total iron concentration by a validated colorimetric method.

Transferrin-bound serum iron dissociates to form ferrous ions at an acidic pH. These ions react with ferrozine (a sulfonated derivative of diphenyltriazine) to produce a water-soluble magenta colored complex with maximum absorption at 560 nm. The difference in color intensity at this wavelength, before and after the addition of ferrozine, is directly proportional to the serum iron concentration. The iron concentration in the unknown samples can therefore be interpolated from a standard curve containing known amounts of iron.

Total iron in human serum (serum iron and Ferrlecit®-bound iron) was quantitated in the same manner except that a suitable reducing agent (sodium hydrosulfite) was added to the samples prior to the addition of ferrozine.

The validated assay range was 50.0 to 2000.0 µg/dL. The LLOQ was 50.0 µg/dL with coefficients of variation over the calibration range from 1.0% to 9.6% (n = 11). The overall accuracy of the method (% nominal concentrations) for the Lower QC, the Medium QC, and the High QC samples (n = 26) was 92.6%, 95.8%, and 92.4%, respectively. The global coefficients of variation (n = 26) for the precision of the method were 7.6%, 5.7%, and 8.8% for LQC, MQC, and HQC samples, respectively.

III. Appendices

A. Ferrlecit PWR

B. Proposed Package Insert (original and Agency proposed)

C. Cover Sheet and OCPB Filing/Review Form

Appendix A

Ferrlecit PWR

NDA 20-955

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

Dear Ms. Frank:

Please refer to your Proposed Pediatric Study Request submitted on November 21, 2001 for Ferrlecit® (sodium ferric gluconate complex in sucrose injection) to NDA 20-955.

To obtain needed pediatric information on sodium ferric gluconate complex in sucrose injection, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following study in pediatric patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy:

- ***Type of study*:**

  The study will be a randomized, double-blind, parallel group, dose-response (two doses) and pharmacokinetic (PK), baseline-controlled trial in pediatric patients with iron deficiency undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy.

- ***Indication to be studied:***

  Treatment of iron deficiency in pediatric patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy.

- ***Age group in which study will be performed*:**

  Pediatric patients age 2 years to <16 years will be studied. Patients of both sexes will be enrolled.

- ***Study Patients***

  1) Number of patients to be studied:

  A minimum of 58 patients (at least 29 in each treatment group) will complete the study (receive study drug and have safety data and efficacy data [baseline and follow-up hemoglobin] documented). A minimum of 12 patients (6 in each treatment group) will complete PK evaluation. The age and sex distribution of patients in the study and in the subset of patients evaluated for PK will be similar to that of these patients in the disease population being studied.

  2) ***Entry criteria:***

  Major inclusion criteria:

  - Male and female pediatric patients undergoing chronic hemodialysis
  - Age 2 to<16 years
  - TSAT < 20% and/or serum ferritin < 100 ng/mL
  - Hgb ≤ 11 g/dL in some patients
  - Receiving a stable erythropoietin dosing regimen (defined as no greater than a 25% change in the patients erythropoietin dose during the 8 weeks before Informed Consent is obtained)

- Informed consent obtained
- Clinically stable

Major exclusion criteria may include:

- Blood transfusion within the 30 days before dosing or at any time during the study
- Hypersensitivity to sodium ferric gluconate complex in sucrose injection product or any of its inactive components
- Pregnancy or lactation

- ***Study endpoints***

The primary efficacy endpoint will be the mean change in hemoglobin from baseline to 14±2 days after administration of the last sodium ferric gluconate complex in sucrose injection dose.

Three repeated measurements of hemoglobin at baseline will be performed to ensure a stable baseline level for comparison. In addition, the pharmacokinetics of sodium ferric gluconate complex will be assessed in each treatment group. Also, the number and percentage of patients who are classified as responders/nonresponders will be summarized for each Ferrlecit dose, with iron deficient patients requiring repletion being classified as responders to treatment if they have an increase in hemoglobin of at least 1.0 gm/dL. Additional, secondary efficacy endpoints may include the mean change in hematocrit, serum ferritin, transferrin saturation, and other indices from baseline to 14±2 days after administration of the last sodium ferric gluconate complex in sucrose injection dose. The mean change in hemoglobin, hematocrit, serum ferritin,

and transferrin saturation from baseline to completion of the final drug administration and at 4 weeks after the last sodium ferric gluconate complex in sucrose injection administration may also be considered as secondary efficacy endpoints.

Blood samples will be obtained every 2 weeks during treatment and followup for determination of hemoglobin, hematocrit, transferrin saturations and serum ferritin to permit assessment of durability of response.

Either a traditional or population PK approach will be used to assess the pharmacokinetics of sodium ferric gluconate complex.

- *Drug information*

Sodium ferric gluconate complex in sucrose injection groups:

Dosage form: Sodium ferric gluconate complex in sucrose injection formulation of appropriate concentration. Prior to initiation of study, evidence must be provided and assessed as adequate by the agency that the maximum amount of bacterial endotoxin and the total amount of benzyl alcohol that will be administered to any patient with the highest assigned dose of sodium ferric gluconate complex in sucrose injection will be safe.

Route of administration: Intravenous infusion

Regimens:

Low dose group: 1.5 mg/kg infused over 1 hour, not to exceed 125 mg per dose, in each dialysis session; during 8 consecutive hemodialysis sessions over approximately 22 days.

High dose group: 3.0 mg/kg infused over 1 hour, not to exceed 125 mg per dose, in each dialysis session; during 8 consecutive hemodialysis sessions over approximately 22 days.

- Concomitant medications

Erythropoietin dose should be held constant as much as possible during the study. If clinically indicated, the erythropoietin dose may be adjusted in order to maintain the patient's Hgb between 10 g/dL and 13 g/dL; Dose adjustments must be documented including date and amount.

- ***Drug specific safety concerns:***

Patients will be monitored closely for anaphylaxis and allergic reactions during and after each drug infusion. Any allergic reaction will be documented and described in detail. For therapeutic infusions, blood pressure and heart rate should be monitored with the patient in the supine position and recorded at baseline before the start of the dialysis session, immediately prior to the start of the sodium ferric gluconate complex in sucrose injection infusion, at about 5 and 15 minutes after initiation of the sodium ferric gluconate complex in sucrose injection infusion, at the end of the sodium ferric gluconate complex in sucrose injection infusion, and at about 15 and 60 minutes after

completion of the sodium ferric gluconate complex in sucrose injection infusion. Resuscitative equipment and procedures must be available for all patients.

- ***Statistical information, including power of study and statistical assessments:***

  The trial will have a detailed statistical plan described in the protocol.

  The trial is designed with 80% statistical power to detect a treatment group difference of 1.0 g/dL in the mean change of hemoglobin from baseline at significance level 0.05, assuming a standard deviation for the change of hemoglobin from baseline of 1.5 g/dL. A minimum of 29 patients in each treatment group is required in the study.

  The primary analysis for efficacy is mean change in hemoglobin from baseline to 14±2 days after administration of the last dose of sodium ferric gluconate complex in sucrose injection. The GLM (general linear model) will be used to adjust for variation in baseline measurement for treatment comparison. For the primary and secondary endpoints, comparison of treatment effect between the two treatment arms also will be done.

  The pharmacokinetic parameters for sodium ferric gluconate complex will be summarized using descriptive statistics. Treatment regimens will be compared with regard to the PK parameters.

- ***Labeling that may result from the study*:**

  Appropriate sections of the labeling may be changed to incorporate the findings of this study.

- ***Format of reports to be submitted*:**

  Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation must be submitted. In addition, information from post-marketing experience in pediatric patients in foreign countries should be included in the integrated summary of safety in pediatric patients.

- ***Timeframe for submitting reports of the study:***

  Reports of the above studies must be submitted to the Agency on or before February 18, 2004. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Submit reports of the studies as **a new drug application (NDA) or as a supplement to your approved NDA** with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request as "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Brian Strongin, R.Ph., M.B.A., Project Manager, at (301) 827-7310.

Sincerely
Yours,

Victor F.C. Raczkowski, M.D., M.Sc.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Appendix B

Proposed Package Insert

Proposed Package Insert: (Sponsor's changes are shown as single underlined text while Agency's proposed changes are shown as double-underlined text)

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. (b) (4)

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

	Mean Change from Baseline to Two Weeks After Cessation of Therapy		
Study A	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

(b) (4)

[redacted]

The primary endpoint was 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 the mean changes 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	
	1.5 mg/kg Ferrlecit® (N = (b) (4))	3.0 mg/kg Ferrlecit® (N = (b) (4))
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

(b) (4)

INDICATIONS AND USAGE

Ferrlecit® (sodium ferric gluconate complex in sucrose injection) is indicated for treatment of iron deficiency anemia in (b) (4) patients undergoing chronic hemodialysis who are receiving supplemental epoetin therapy.

CONTRAINDICATIONS

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

WARNINGS

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

PRECAUTIONS

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

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

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

of intravenous iron. These hypotensive reactions are not associated with signs of hypersensitivity and have usually resolved within one or two hours. Successful treatment may consist of observation or, if the hypotension causes symptoms, volume expansion. See ADVERSE REACTIONS.

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

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

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

Pediatric Use: Ferrlecit® was shown to be safe and effective in patients ages 6 to 15 years (refer to CLINICAL STUDIES section). Safety and effectiveness in pediatric patients (b) (4) 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 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%). (b) (4)

[redacted]

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.

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

February 2004.

Appendix C

Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**20-955 / SE5-006**	**Proposed Brand Name**	**Ferrlecit**
OCPB Division (I, II, III)	**II**	**Generic Name**	**Sodium Ferric Gluconate Complex in Sucrose Injection**
Medical Division	**GI & Coagulation**	**Drug Class**	**Anti-anemic**
OCPB Reviewer	**Suliman Al-Fayoumi**	**Indication(s)**	**Iron Deficiency Anemia**
OCPB Team Leader	**Suresh Doddapaneni**	**Dosage Form**	**Injection**
		Dosing Regimen	**1.5 mg/kg elemental iron infused over 1 hour**
Date of Submission	**2/13/04**	**Route of Administration**	**I.V.**
Estimated Due Date of OCPB Review	**6/15/04**	**Sponsor**	**Watson Laboratories, Inc.**
PDUFA Due Date	**8/13/04**	**Priority Classification**	**Priority**
Estimated Division Due Date	**7/6/04**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	**1**	**1**	**1**	
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				

PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses –				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**1**	**1**	**1**	

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	**X**	
Comments sent to firm ?	**Not needed at this time**	
QBR questions (key issues to be considered)	**1. Do the findings of the PK study support the proposed dosage recommendations in pediatric patients aged 6-16 years?**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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

/s/

Suliman Alfayoumi
8/2/04 03:31:12 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
8/2/04 03:34:20 PM
BIOPHARMACEUTICS