DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

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*:**

  This will be a randomized, double-blind, parallel group, dose-response (using two doses) pharmacokinetic (PK) study 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) should complete the 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 patients in the disease population being studied.

  2) ***Entry criteria:***

     Major inclusion criteria:

     - Pediatric patients undergoing chronic hemodialysis
     - TSAT < 20% and/or serum ferritin < 100 ng/ml
     - 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)
     - Clinically stable

- ***Study endpoints***

  - The primary efficacy endpoint will be the mean change in hemoglobin from baseline to two weeks. This two-week measurement will be taken between 12 and 16 days after administration of the last dose of sodium ferric gluconate complex in sucrose injection. Usually, three

repeated measurements of hemoglobin at baseline will be performed to ensure a stable baseline level for comparison.

- The number and percentage of patients who are classified as responders/nonresponders will be summarized for each dose group, with iron deficient patients requiring repletion being classified as responders to treatment of they have an increase in hemoglobin of at least 1.0 gm/dl.
- Secondary efficacy endpoints may include the mean change in hematocrit, serum ferritin, and transferrin saturation from baseline to two weeks after administration of the last dose of sodium ferric gluconate complex in sucrose injection.
- Blood samples will be obtained in most patients four weeks after the last dose of sodium ferric gluconate complex in sucrose injection for determination of hemoglobin, hematocrit, transferrin saturation, and serum ferritin to permit assessment of durability of response.
- The pharmacokinetics of sodium ferric gluconate complex will be assessed in each treatment group.
- Adverse Events (AEs) will be tabulated and recorded.

- ***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 the 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**

The erythropoietin dose should be held constant as much as possible during the study. Dose adjustments must be documented including the date and amount of the change.

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

Patients will be monitored closely for anaphylaxis and allergic reactions or hypotension that is unrelated to anaphylaxis during and after each drug infusion.

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

  - The primary analysis for efficacy will be the comparison, between the two treatment groups, of the mean change in hemoglobin from baseline to two weeks after administration of the last dose of sodium ferric gluconate complex in sucrose injection. 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 a two-sided significance level of 0.05, assuming a common standard deviation of 1.5 g/dl for the change in hemoglobin from baseline. A minimum of 29 patients in each treatment group is required in the study.

- Efficacy in the treatment groups will be compared to the response in a relevant pediatric historical control.

- ***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. 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. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities.

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

Reports of the above studies must be submitted to the Agency on or before August 9, 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.

- ***Response to Written Request:***
  As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

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 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

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

/s/

Victor Raczkowski
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