CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020955

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

REQUEST FOR TRADEMARK REVIEW

957

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Gastrointestinal and Coagulation Drug Products	**HFD-180**
Attention: Brian Strongin	**Phone:** (301) 443-0483
Date: January 21, 1998	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: Ferrlecit ® Injection	**NDA#** 20-955
Established name, including dosage form: Sodium ferric gluconate complex in sucrose injection	
Other trademarks by the same firm for companion products: None	
Indications for Use (may be a summary if proposed statement is lengthy): Ferrlecit® is indicated as first line treatment for iron deficiency anemia in renal hemodialysis patients on supplemental recombinant human erythropoietin.	
Initial Comments from the submitter (concerns, observations, etc.): No concerns at this time.	

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original 20-955; HFD-180/division file; HFD-180/B.Strongin; HFD-180/R.Frankewich

Rev. December 95

APPEARS THIS WAY ON ORIGINAL

Consult #957 (HFD-180)

FERRLECIT sodium ferric gluconate complex in sucrose injection

The Committee noted sound-alike/look-alike conflicts between FERRLECIT and the following marketed products: FERRALETS and FEROLIX. The committee felt there was a low potential for mix-up with this product since they have different strengths, and indications. There were no misleading aspects found.

However, if this product is a true complex that behaves as a single entity, it is recommended that the sponsor seek a USAN for the complex.

The Committee has no reason to find the proposed proprietary name unacceptable.

/S/ [redacted] 3/6/98, Chair
CDER Labeling and Nomenclature Committee

APPEARS THIS WAY
ON ORIGINAL

GREENBERG
ATTORNEYS AT LAW
TRAURIG

ORIGINAL

NEW CORRESP

Jur Strobos
202/331-3150

February 24, 1998

Dr. Lilia Talarico
Division of Gastrointestinal & Coagulation Drug Products
PKLN 6B45 HFD-180
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Application: NDA 20-955
Ferrlecit® (sodium ferric gluconate complex in sucrose) Injection
R&D Laboratories, Inc.
Amendment 003

Dear Dr. Talarico:

This amendment requests a categorical exclusion from the requirement to submit an environmental assessment (EA) per 21 C.F.R. § 25.31(b). Further, on behalf of my client, R&D Laboratories, Inc., we request that the abbreviated EA submitted with NDA 20-955 be withdrawn.

The expected introduction concentration (EIC) entering into the aquatic environment from patient use, assuming all drug substance produced is used, is approximately [redacted] ppb which is will be [redacted] ppb limit for eligibility for categorical exclusion under 21 C.F.R. § 25.31(b).

Thank you for your assistance.

Sincerely,

Jur Strobos

GREENBERG TRAURIG HOFFMAN LIPOFF ROSEN & QUENTEL
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1300 CONNECTICUT AVENUE, N.W.
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MIAMI FORT LAUDERDALE WEST PALM BEACH TALLAHASSEE ORLANDO
NEW YORK WASHINGTON, D.C.

NDA 20-955

R & D Laboratories, Inc.
Attention: Rhoda Makoff, Ph.D.
4640 Admiralty Way, Suite 710
Marina del Rey, CA 90292

JUN 30 1998

Dear Dr. Makoff:

Please refer to your new drug application (NDA) dated December 30, 1997, received December 30, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferrlecit® (sodium ferric gluconate complex in sucrose injection) 62.5 mg/5ml.

We acknowledge receipt of your submissions dated, December 30, 1997, January 7, 16, 23, 26, and 28, February 5, 6, 9, 13, and 24, March 9, and 12, April 6, 15, 17, 28, and 29, May 8, 9, and 21, and June 2, 9, and 16, 1998.

The user fee goal date is June 30, 1998.

We have completed the review of this application as submitted with draft labeling and it is approvable. Before the application may be approved, however, it will be necessary for you to submit the following information:

Chemistry, Manufacturing, and Controls

1. During a recent inspection of the [redacted] drug product manufacturing facility for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the inspector. Satisfactory inspections will be required before this application may be approved.

2. The stability data submitted does not support the proposed expiration date of 36 months. Data to support the expiration date must come from the primary stability batches, that is, the data that include the full battery of current specifications. Data from batches 7H791, 7H792, and 7H829 meet these requirements; however, only three months real-time data [redacted] has been submitted. If it could be shown by statistical analysis that specifications for all parameters were likely to be met after twelve months for all batches, then a recommendation for a 12-month expiration date might be possible; data from the other batches (TH40963, 4L0321, 4L0319, 4P0428, and 5B219) could then be used to support this. However, linear regression analysis of the data submitted from the primary batches indicates that for several parameters [redacted] the projected expiration date is far short of twelve months.

Please submit available stability data and provide linear regression analysis of batches 7H791, 7H792, and 7H829 using the SAS program. A new expiration date should be proposed based on this data. The data from the other batches should be used as a confirmation of the proposed new expiration date.

3. Data which supports labeling recommendations for the acceptable length and condition of storage of diluted drug product is needed. Dilution stability studies should be conducted to generate this data.

4. It is noted, in the validation experiments for the [redacted] method, that the procedure was applied to a laboratory prepared sample of the formulation [redacted] titre obtained was the same as that for the blank. Clarification of the validation experiments is needed to determine the specificity of this method. Specifically, the following should be provided: the specific composition of the sample; the number of repetitions of the test performed; the actual titer volumes; and, most importantly, the composition of the blank used.

5. In the validation of linearity in the method for [redacted] the procedure was performed on aliquots of different size taken from a Ferrlecit® sample. Clarify whether or not all of these samples were diluted to the same volume before the [redacted] procedure was performed, and if they were, what the diluent was.

6. No system suitability procedure is described for the [redacted] method for [redacted]

7. Regarding the validation of the method for [redacted] describe exactly how the molecular weight of a Ferrlecit® sample is calculated using the calibration curve generated from the eleven molecular weight standards. If a mathematical equation is generated for the calibration curve, it should also be described.

8. Regarding the validation of the method for the determination of [redacted] for accuracy: clarify how the [redacted] was achieved. Lot No. 66721, which was the Ferrlecit® lot used for the experiment, apparently is a typical batch of Ferrlecit®, with a nominal [redacted]

9. Provide the validation of the specificity of the [redacted] method. Please provide a discussion of possible interferants with this method, and how this method would serve to ensure that the analyte is properly separated from them. If no validation for specificity is necessary, justification should be provided.

10. Regarding the demonstration of linearity for the [redacted] Method:

a. Demonstrate linearity with a minimum of five (5) concentrations.

b. Please provide a plot of the data.

11. Provide the suitability procedure for the [redacted] method for [redacted] A system suitability procedure should be established such that factors such as tailing factor, capacity factor or retention time of the main peak (and perhaps resolution of the main peak and some resolution probe compound) are given standard values that the [redacted] system must meet each time it is set up to run this procedure.

12. In the validation data provided for the [redacted] method for [redacted] no [redacted] provided. No indication is provided regarding what the retention time, shape or capacity factor of the [redacted] is. Submit [redacted] of some of the runs described within the data.

In addition, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed marked-up draft labeling. Please note that, although no fatal anaphylactic reactions have been reported with Ferrlecit®, the professional labeling should retain the boxed warning associated with the administration of parenteral iron preparations since anaphylactic reactions have occurred with Ferrlecit® and reporting compliance of all events has not been established. It will also be necessary for you to revise the immediate container and carton labeling submitted April 6, 1998 as follows:

Foil-on-Tray Label

Please add the following information to the foil-on-tray label:

1. the name and place of business of the manufacturer, packer, or distributor;

2. the statement "Rx Only";

3. a statement of the usual or recommended dosage or a statement such as "See package insert for dosage information";

4. the established names and quantities of inactive ingredients;

5. placement of an identifying lot or control number;

6. placement of an expiration date;

7. and a statement of the appropriate storage conditions.

Ampule Label

Please add the following information to the ampule label:

1. the statement "Rx Only";

2. the established names and quantities of inactive ingredients;

3. placement of an identifying lot or control number;

4. placement of an expiration date;

5. and a statement of the appropriate storage conditions.

Please submit 20 copies of the printed labels and other labeling, ten of which are individually mounted on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

1. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs now will certainly facilitate review.

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings, if any.

4. Summarize worldwide experience on the safety of this drug.

5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

Although not required for approval, we request that you provide the following at your earliest convenience:

1. Regarding the dialysis experiments done to elucidate the role of [redacted] in Ferrlecit®, indicate whether or not the removal of the sucrose follows a linear pattern over time. Please provide data which shows the removal rate.

2. Certificates of Analysis (COAs) are provided for three lots of Sucrose BP Gran; these are identified as RPR lot nos. 9402939, 9403015, and 9710881. The COAs indicate that the full battery of tests were not performed on lots 9402939 and 9403015. In both cases, the following tests were omitted: Conductivity; Foreign [redacted] Loss on Drying (LOD); and Bacterial Endotoxins. Please: 1) explain the circumstances under which the full battery of tests will be performed; and 2) justify a raw material testing scheme that does not require the full battery of tests on each batch.

3. On the [redacted] Quality Control Specification for [redacted] which is provided on pg. 169 of Volume 1.2 of the Application, the assay value is [redacted] However, on both of the COAs for two different lots of this compound, the specification for the assay value is given as [redacted] Please clarify this, and please ensure that all documents pertaining to the testing of this raw material are consistent.

4. Provide a description of the drug product sampling plan for product release testing. The description should include:

   - the number of units produced per batch;
   - the number of units subjected to finished product testing;
   - a description of the process by which the units are sampled (i. e. is it governed by statistical considerations or is it random; are samples selected at certain points during production such as beginning, middle, end, etc.);
   - and a description of the process by which the number of units subjected to finished product testing is chosen.

5. In the summary table of Regulatory Specifications and Analytical Methods provided on page 39 of Volume 1.2 of the Application, one of the tests listed is Identity - [redacted] The specification for this parameter is NMT [redacted] and it is listed as being among the methods in document R7858. In the actual document R7858, which is provided starting on page 11 of Volume 1.3 of the application, this test and specification are not listed. In the actual method procedure for the Identity test, given in the same document, [redacted] is assessed qualitatively, but not quantitatively. An explanation should be provided.

6. Regarding the method for determination of weight per mL, describe how the sample temperature is maintained in the syringe used to inject the sample and in the instrument after sample injection.

7. Regarding the procedure for [redacted] please clarify the role of starch. Please confirm that: 1) the endpoint of this titration is a clear solution; and 2) that starch is used not as an indicator, but as a color enhancement agent for the species being titrated (iodine). If the above is not the case, then please provide a complete description of the chemical reactions involved in this procedure.

8. Regarding acceptance testing of the container /closure system: please clarify how sampling will be performed for acceptance testing on the ampoules. Full specification testing is to be performed on a batch of ampoules received from the manufacturer (every 1 in ten batches, according to the submission). In the [redacted] acceptance specifications and methods for ampoules provided in Appendix B.6.3.2 (pp. 265-272 of Volume 1.2), for the Visual Inspections for Defects test, a detailed sampling and inspection plan based on BS 6001 (which is equivalent to [redacted], based on [redacted] levels) is provided. Please clarify whether or not this procedure will also be used when full specification testing is done. Also, for the batches in which full specification testing is not done, it is noted in section B.6.3 (*Container-Closure System*, pg. 35 of Volume 1.2) that "visual identification" and color ring coding check tests will be done. Please clarify if "visual identification" is in fact the Visual Inspections and Defects test, with the detailed sampling and analysis plan, as described in the [redacted] specifications and methods for ampoules.

9. It is recommended that the storage statement be changed to "Store at 25 °C (68 °F); excursions permitted to 15-30 °C (59-86 °F). See USP Controlled Room Temperature."

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your options under 21 CFR 314.110. In the absence of such an action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment not will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Brian Strongin, Project Manager, at (301) 443-0483.

Sincerely yours,

/S/ [redacted] 6/30/98

Paula Botstein, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ATTACHMENT

R&D Laboratories, Inc.
4640 Admiralty Way, Suite 710
Marina del Rey, California 90292 USA
TEL: 310-305 8053 • 800-338-9066 • FAX: 310-305-8103
E-MAIL: rndlabs@aol.com • INTERNET: http://www.rndlabs.com/rndlabs

Jur Strobos
202/518-6377

February 8, 1999

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA # 20-955
R&D Laboratories, Inc.
Ferrlecit® (ferric sodium gluconate complex in sucrose injection)
Correspondence

Dear Dr. Talarico:

This letter responds to FDA's request for commitment to specific post-approval submissions relating to the chemistry section. This letter represents a commitment to those requirements. More specifically, R&D Laboratories, Inc., commits to clarification of the identified issues with regard to calibration for the Apparent Molecular Weight Assay and with regard to packaging component test procedures.

Additionally, we commit to prior approval submission, as a supplemental application, of any initial expiration extension supported by new stability data available to support such extension of the 12 month expiry. The above-referenced NDA contains an approved stability protocol within the meaning 21 C.F.R. § 314.70(d)(5). We understand that FDA will review these data expeditiously given the difficulty that a small business entity may have in marketing a drug product with 12-month expiry. We understand that FDA will be able to provide a response within four months of submission.

Sincerely,

Jur Strobos, MD

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Jur Strobos
202/518-6977

December 30, 1998

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA # 20-955
R&D Laboratories, Inc.
Ferrlecit® (ferric sodium gluconate complex in sucrose injection)
Amendment # 24

Dear Dr. Talarico:

This letter responds to FDA's request of November 2, 1998, for commitment, in writing, to specific post-approval phase IV studies and anticipated timeframes for initiation and completion of studies as well as the anticipated time of submission of a final study report.

Please note that the provided timelines are based on assumptions which may include: (1) FDA review and comment will not exceed 60 days (the time allocated for review of a newly filed IND plus an additional 30 days as recommended by the Consumer Safety Officer); (2) potential revisions of protocols in light of such comments can be undertaken within a few weeks; (3) any revisions requested do not significantly increase the number of patients to be enrolled and/or the treatment or observational period required for each patient; (4) any revisions do not significantly change inclusion or exclusion criteria to a more restrictive or less available patient population; (5) subsequent IRB submission, review, and approval of final protocols is timely and uncomplicated; (6) FDA does not require any waiting period before initiation of the study after final filing to IND [redacted] (7) under the final protocol inclusion and exclusion criteria, sufficient patients are enrolled in a timely fashion to meet anticipated deadlines; and, (8) specifically with regard to pediatric studies, a Written Request for Pediatric Studies is received before approval if such a request letter is deemed necessary to entitle R&D Laboratories, Inc., to six months of exclusivity related to pediatric studies or FDA confirms that the request in the November 2 letter meets statutory criteria for such exclusivity.

R&D Laboratories, Inc., hereby, commits in writing to the performance of the following studies as enumerated and described below:

ORIGINAL

1. A Segment I intravenous fertility and reproductive performance study in the rat.

This study will consist of three treatment groups and 1 vehicle control group (26 rats per sex per group). The test article will be administered intravenously as a single daily dose at approximately the same time each day. Dose levels for this study will be 1, 5, and 10 mg Fe/kg. These doses are based on the results of previous Segment II and III studies. Test article administration to males will begin 28 days prior to mating and continue until euthanasia. Administration to females will begin 14 days prior to mating and continue through Day 7 of gestation (implantation). The females will be paired with males from the same dose group and observed daily for evidence of copulation which will be day 0 of gestation. The duration of the study will be approximately nine weeks. Observations for clinical signs, body weights, and food consumption measurements will be recorded during the study period. Beginning 10 days prior to mating, the females will be examined daily to evaluate estrous cycling. Uterine examinations of dams will be performed on Day 13 of gestation. Gravid uterine weight and the weight of the ovaries will be recorded. Total number of corpora lutea and implantations, location of early and late resorptions, and viable and nonviable embryos will be recorded. Following disposition of females, males will be euthanized and subjected to necropsy, and any findings will be recorded. The testes and epididymides will be weighed, and analysis of sperm (concentration, motility, and morphology) will be performed. Reproductive organs and gross lesions will be fixed for possible microscopic evaluation.

Study Initiation	No later than two months following approval
Study Completion; Submission of Final Report	No later than nine months following initiation

In Amendment #23, dated December 28, 1998, we have already provided a more complete description of the proposed study for FDA review and comment, as requested in the FDA letter of November 2, 1998, before submission of a final protocol to IND # [redacted]

2. A 13 week intravenous subchronic toxicity study in the dog.

There are limited data available in the dog on which to select doses for the 13 week study. Previous studies suggest that the LD_{50} is approximately 262 mg/kg. Initially, a range finding study will be performed with an initial dose level of 100 mg Fe/kg.

a. Range Finding Study

This study will consist of one treatment group (2 males and 2 females). The test article will be dosed intravenously to each animal at an initial level of 100m Fe/kg. Observations for clinical signs, body weights, and food consumption will be measured. Two or three days later, the dogs will be redosed at a specified level either higher or lower than the initial dose, depending on the results noted following the first dose. This procedure (dosing the one group of dogs with successive doses every 2-3 days) will continue until a maximum tolerated dose is achieved. Then, all four dogs will be dosed for seven consecutive days at a suitable dose level. Blood samples will be collected at specified intervals, and plasma sent for analysis of drug

concentrations. Gross necropsies will be performed on all animals found dead and on animals at scheduled and unscheduled sacrifice.

b. Intravenous Toxicity Study

Following completion of the aforementioned study, this study will consist of 3 treatment groups and 1 control group (3 animals/sex/group). The test article will be dosed intravenously for 91 consecutive days. Observations for clinical signs, body weights, and food consumption will be measured during the course of the study. At the end of the exposure period, hematological, serum biochemical and urinalysis evaluations will be conducted. At termination, organ weight, macroscopic and microscopic pathology will be conducted.

Study Initiation	No later than two months following approval
Study Completion; Submission of Final Report	No later than ten months following initiation

In Amendment #23, dated December 28, 1998, we have already provided a more complete description of the proposed studies for FDA review and comment, as requested in the FDA letter of November 2, 1998, before submission of a final protocol to IND # [redacted]

3. A pilot human pharmacokinetic study of Ferrlecit®.

We hereby commit to the performance of the study protocol, entitled "Open-Label, Dose Ranging Study to Determine the Single-Dose Pharmacokinetics of Ferrlecit® (Sodium Ferric Gluconate Complex in Sucrose Injection) Following Intravenous Administration to Healthy, Iron Deficient Volunteers," submitted for FDA review and comment as part of Amendment #23, dated December 28, 1998, and before submission to IND [redacted] This study is henceforth identified as **FER9801**.

Study Initiation	No later than three months following approval
Study Completion	No later than two months following initiation
Final Report Submission	No later than three months following study completion

4. A study to determine the optimal dosing regimen for patients requiring repeated courses of Ferrlecit for the achievement of iron repletion and for the maintenance of iron repletion.

We hereby commit to the following study, subject to ongoing consultation on endpoints and dosing ranges with appropriate experts, which will henceforth be identified as Study No. **FER9805**:

Study Title	Dose-Ranging Study for Ferrlecit® (Sodium Ferric Gluconate Complex in Sucrose Injection) as Empiric Maintenance Therapy in Hemodialysis Patients on Epoetin Following Iron Repletion Therapy

Objectives	Evaluate the safety and efficacy of two maintenance doses v. oral iron in repleted hemodialysis patients.
Patient Population	Inclusion Criteria: • Adult male or female hemodialysis patient able to comprehend and provide written informed consent. • Chronic hemodialysis therapy>3 months • Chronic epoetin therapy>2 months • Iron repleted by administration of 1 gm series with a 2 week period of no iron therapy before assay of iron repletion parameters as *infra*. • Iron replete defined as: - Serum ferritin>100 ng/mL - TSAT>20% - Hgb>11 g/dL but ≤ 12.0 g/dL Exclusion Criteria: • Known sensitivity to Ferrlecit® or epoetin • Ferritin>800 ng/mL • TSAT>50% • Blood transfusion in preceding 60 days • Serum albumin<2.5 g/dL • Signs or symptoms of infection • Unstable angina pectoris or evolving MI • Malignancy • Signs or symptoms of acute peripheral vascular ischemia • Signs or symptoms of acute cerebrovascular insufficiency • Scheduled living donor transplant • Failed transplant in last 6 months • Hospitalization in preceding 30 days
Number of Subjects	≈150; 50 per dose group
Study Sites	≈15
Treatment Regimens	A. Ferrlecit® 62.5 mg q. week for 6 months B. Ferrlecit® 31.3 mg q. week for 6 months C. Ferrous SO_4 325 mg (65mg Fe) t.i.d./6 months Epoetin dose adjusted based on the following hemoglobin (g/dL) criteria: <10.0 Increase epoetin by 25% 10-10.9 Increase epoetin by 10% 11.0-12.0 No change 12.1-13.3 Decrease epoetin by 10% 13.4-15.0 Decrease epoetin by 25% >15.0 Hold epoetin for one dose and resume at 50% of dose

Efficacy Variables	1°—Percentage of failures defined as: No. of patients not completing 6 months of protocol when failure is based on reduction of hemoglobin at two consecutive weeks by > 1gm/dL from baseline or two consecutive sequential epoetin increases separated by 2 weeks that have increased dose by 20% from baseline. 2°—Δ in Hgb, Hct, Epo dose change, TSAT, ferritin, CHr
Safety Variables	Laboratory tests, vital signs, subjective complaints
Statistical Analysis Plan	Fishers Exact test to compare failure rates and survival analysis to compare the time to failure among the three groups.

Study Initiation	No later than eight months following approval
Study Completion	No later than 13 months following initiation
Final Report Submission	No later than 8 months following completion

5. A study to determine the safe and effective dosing regimen in the pediatric patient population.

Preliminary Discussion

FDA has formally requested, in the letter of November 2, 1998, the performance of a pediatric study. In accordance with section 111 of the Food and Drug Administration Modernization Act of 1997 (Pub. L. No. 105-115), 21 U.S.C. § 355A (FDAMA), and the current response to that letter, which includes specific timelines for these pediatric studies, *infra*, we believe that the sponsor has completed the preliminary requirements which would entitle R&D Laboratories, Inc., to an additional six months of exclusivity for a new chemical entity.

However, pursuant to Guidance for Industry entitled "Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug and Cosmetic Act," FDA has set forth supplemental conditions for entitlement to exclusivity. In particular, the Guidance requires the submission of a request for an official Written Request for Pediatric Studies which must allow sufficient time for FDA to review the submitted protocols.

While we do not agree with the necessity for this submission as a predicate to entitlement to additional exclusivity under FDAMA, the sponsor will file a request for an official Written Request for Pediatric Studies, which will include completed draft pediatric study protocols suitable for FDA review and comment, as Amendment #25 within 7 days of this Amendment. We believe that this filing will permit FDA sufficient time to review the protocols and issue an official Written Request before the anticipated February 18, 1999, Office Action on NDA 20-955. While we believe that it would be important for an official Written Request to issue before an approval action, we understand that regardless of whether such a Written Request is issued,

Ferrlecit® would be entitled to an additional six months of exclusivity if the studies are accepted. If this is not correct, please advise us immediately.

Response to Request for Pediatric Safety and Efficacy Study

We have evaluated FDA's request in light of specific subpopulations identified in the proposed rule governing pediatric patients, 62 FR 43900 (Aug. 15, 1997), and the guidance entitled, "General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products." 63 FR 66632 (Dec. 2, 1998).

We request a full waiver for two pediatric subpopulations: neonates (birth to 1 month) and infants (1 month to 2 years). We hereby commit to perform separate clinical studies in the remaining subpopulations subject to issuance of an official Written Request for Pediatric Studies or other determination of entitlement to additional exclusivity.

A. Request for Waivers

i. Neonates (birth to 1 month)

Ferrlecit® contains benzyl alcohol as an inactive ingredient at a level of 9.0 mg/mL (0.9%). Benzyl alcohol is contraindicated in neonates. Therefore, we certify the administration of Ferrlecit® would be unsafe in this age group. To that end, final labeling cautions that "Ferrlecit® contains benzyl alcohol and therefore should not be used in neonates."

In May 1982, FDA issued a letter to more than 50,000 pediatricians, pharmacists, and hospitals with a warning about potential fatal benzyl alcohol poisoning attendant to the administration of solutions containing 0.9% benzyl alcohol. The warning letter was issued following publication of an article in New England Journal of Medicine which described a "gasping syndrome and benzyl alcohol poisoning."[1] The average dose of fatal reactions was estimated to be 191 mg/kg/day or, if the drug product had been Ferrlecit® administered to a one pound neonate, about 10 mLs or 125 mg of elemental iron. A reported minimum intake calculated to produce a toxic reaction was 130 mg/kg/day or about 6.5 mLs of Ferrlecit® administered to a one pound neonate.

We have attached a copy of the NEJM article, the relevant FDA Drug Bulletin, a notice published in Morbidity Mortality Weekly Reports, and several additional references from which the aforementioned date were derived at Tab A.

ii. Infants (1 month to 2 years)

We hereby certify that the necessary studies are impossible or impractical in this pediatric subpopulation because the total number of such patients is too small and geographically

[1] Gershank J, Boecler B, Ensley J, McCloskey S, George W. The Gasping Syndrome and Benzyl Alcohol Poisoning. NEJM 307:1384-1388 (1982).

dispersed. Ferrlecit® is not likely to be used in a substantial number of patients in this age group. The reported incidence of End Stage Renal Disease (ESRD) in patients between 0 and 4 years old is reported as between 9 and 25 patients per year per million population. *See* attached data from the U.S. Renal Disease Survey at Tab B. Thus, assuming an equal distribution between 0 and 4, the number of infant patients less than 2 years old with ESRD, including transplanted patients, in the entire U.S. is on the order of 1,250 to 3,125. Any single population center (Metropolitan Statistical Area [MSA] $\geq$ 10 million) which could serve as a center for such a study would have 13 patients at most within the entire MSA who would be scattered among multiple dialysis centers or hospital facilities. Further, the incidence of chronic hemodialysis treatment resulting in clinically significant iron deficiency among this population is unknown, given existing priority for transplantation. Even if the incidence parallels that in adult hemodialysis patients (60%), then a maximum annual total US exposure would be less than 2000 infants. Thus, not only is it not feasible to conduct a safety and efficacy study in such patients, but too few patients would be ever be exposed to represent a substantial number to justify such a study. Finally, we believe that the study in children described *infra* (FER9804) may potentially provide sufficient information that will be useful to clinicians managing hemodialysis patients in the higher age range of the infant subpopulation.

B. Studies

i. Children (2 to 12 years)

We hereby commit, as noted *supra*, to perform the FDAMA requested study (hereinafter, FER9804) and seek FDA agreement on study design and timelines for completing the study in an official Written Request for Pediatric Studies. We believe that this study, to ensure the safe administration in this patient population, should properly be commenced and dosages finally identified following completion of study FER9801 and the interim data analysis from the FER9803 study. The results of study FER9801 will permit optimization of blood sampling times to avoid excessive blood drawing in study FER9804. The interim analysis of the FER9803 study will evaluate the safety of Ferrlecit® in about 1100 adult patients. We believe that knowledge of these data will help investigators further protect the children enrolled in study FER9804. A description of protocol FER9804 follows:

Study Title	Open-label, Controlled, Randomized, Multicenter, Comparative Study of the Safety and Efficacy of Two Doses of Ferrlecit® (Sodium Ferric Gluconate Complex in Sucrose Injection) Versus Oral Iron in the Treatment of Iron Deficiency in Childhood Hemodialysis Patients on Epoetin
Patient Population	Inclusion Criteria: • Pediatric male or female hemodialysis patient distributed between 2-12 years of age. • Chronic hemodialysis therapy>3 months • Chronic epoetin therapy>2 months • Iron deficiency anemia defined as: - Serum ferritin<100 ng/mL - TSAT<20% - Hgb<11 g/dL Exclusion Criteria: • Hospitalization in preceding 30 days • Sensitivity to Ferrlecit® or epoetin • Blood transfusion or oral iron supplementation in preceding 30 days • TSAT>50%; ferritin>800 ng/mL • Serum albumin<2.5 g/dL • Signs or symptoms of infection • Malignancy • Scheduled living donor transplant • Failed transplant in last 6 months.
Number of Subjects	≈120 dispersed in age range; 40 per dose group
Study Sites	≈15-25
Treatment Regimen	A: <30 kg = 4 mg/kg Ferrlecit® x 8 doses; ≥ 30 kg = 125 mg Ferrlecit® x 8 doses. B: <30 kg = 2 mg/kg; ≥30 kg = 62.5 mg Ferrlecit® x 8 doses. C: Ferrous sulfate at 6mg/kg/d t.i.d. iron.
Efficacy Variables	1^0—Δ in hgb at 42 days post first dose. 2^0—Δ in hct, epoetin dose, TSAT, ferritin, CHr
Safety Variables	Laboratory studies, vital signs, adverse events, subjective complaints.
Statistical Analysis Plan	To Be Determined

Study Initiation	No later than two months following submission of interim analysis from FER9803.
Study Completion	No later than 26 months after study initiation
Final Report Submission	No later than 6 months after study completion

ii. Adolescents (12 years to <16 years)

In adolescents, the course and management of iron deficiency is similar to that in adults patients as recognized in textbooks of hematology. We hereby commit to perform the following FDAMA requested study (hereinafter, **FER9802**) and seek FDA agreement on study design and timelines for completing the study in an official Written Request for Pediatric Studies. We believe the results of study FER9801 are necessary for the final design of FER9802's points for assessments to preclude excessive or unnecessary blood drawing. Therefore, study FER9802 cannot commence until evaluation of the FER9801 study results.

Study Title	Open-Label Study for Single-Dose Pharmacokinetics of Ferrlecit® (Sodium Ferric Gluconate Complex in Sucrose Injection) Following Intravenous Administration to Adolescent Hemodialysis Patients on Epoetin.
Patient Population	Inclusion Criteria: • Pediatric male or female hemodialysis patient distributed between 12 to ≤16 years of age. • Chronic hemodialysis therapy>3 months • Chronic epoetin therapy>2 months • Iron deficiency defined as: - Serum ferritin<800 ng/mL - TSAT<50% - Hgb<11 g/dL • Non-smoking Exclusion Criteria: • Presence of significant intercurrent illness • Sensitivity to Ferrlecit® or epoetin • Blood transfusion or oral iron supplementation in preceding 30 days
Number of Subjects	8 (with distribution through age range)
Study Sites	1
Treatment Regimen	125 mg of Ferrlecit® administered over 60 minutes.
Efficacy Variables	1°-Serum AUC_{0-t}, AUC_{inf}, C_{max}, t_{max}, k_{el}, V_d, Cl 2°-ferritin, TSAT
Safety Variables	Vital signs, subjective complaints
Statistical Analysis Plan	*See* FER9801 Protocol Submission

Study Initiation	No later than one month following submission of final study report for FER9801
Study Completion	No later than six months following initiation
Final Report Submission	No later than three month following study completion

Completed draft protocols of the foregoing studies will be submitted as part of Amendment #25 which shall represent a formal sponsor Request for an official Written Request for Pediatric Studies for FDA review and comment.

*6,7. **A study to provide additional safety data . . . and gathering additional information (i.e., literature reports, adverse drug reaction reports) concerning the possibly increased risk of allergic/anaphylactic reactions inpatients receiving ACE inhibitors and Ferrlecit concurrently.***

We hereby commit to the performance of the two study protocols as previously submitted for FDA review and comment as part of Amendment # 23 (hereinafter, **FER9803** and **FER9806**). These studies address the need for additional safety data and gathering additional information with regard to reactions in patients receiving ACE inhibitors. The sponsor hereby commits to the following time frames contingent on receipt of comments on the study designs found in Amendment # 23 no later than January 30, 1999, and FDA permission to initiate the studies FER9803 and FER9806 simultaneously with filing of final amended protocols that reflect FDA comments to IND [redacted]

As requested in teleconference with the Division, we agree that initiation of these studies no later than at product launch is critical to their success. Following launch, the number of Ferrlecit® naïve patients will be significantly reduced especially those sensitive to iron dextran. Additionally, incentives for participation in studies are significantly reduced for both patients and investigators following commercial availability.

Thus, we request that FDA expedite its review of these protocols as submitted in Amendment #23.

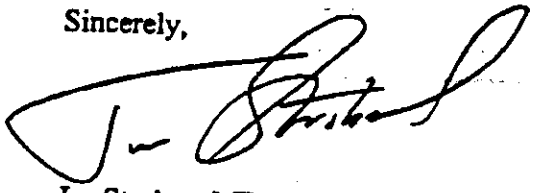
	FER9803	FER9806
Study Initiation	On or before launch (projected for April 5, 1999)	On or before launch (projected for April 5, 1999)
Study Completion	No later than 7 months following initiation	No later than 16 months following initiation
Final Report Submission	No later than 5 months following completion	No later than 5 months following completion

Conclusion and Summary of Requested Office Actions

Based on the instant commitment to each specified study, we respectfully request approval of Ferrlecit® for marketing and written confirmation that, among the studies to which we have committed, studies FER9802 and FER9804 represent FDAMA requested studies within the meaning of the opening paragraph of § 505A(a) of the Food, Drug and Cosmetic Act.

Alternatively, we request in response to Amendment #25, an official Written Request for Pediatric Studies. We additionally request clarification as to whether R&D Laboratories, Inc., may be entitled to one or two periods of additional six months of exclusivity related to pediatric studies. Finally, we request expedited review and comment on studies FER9803 and FER9806 so that they can be commenced on launch. We believe that all issues identified in the approvable letter dated June 30, 1998, and subsequent correspondence have been finally resolved and that NDA 20-955 is in condition for approval.

Sincerely,



Jur Strobos, MD

NB.: For the sake of ease of comprehension, we have appended a chart which outlines the timelines for all studies at Tab C under the assumption of an approval on or before February 18, 1999 and that the sequence of studies can be conducted as planned.

Enclosures:

Tab A – references on benzyl alcohol toxicity
Tab B – references on infant ESRD patient population
Tab C – graphical depiction of timelines of phase IV studies

Finally, measurement of pulmonary-artery pressures should be read from the pressure wave form at the end of expiration, without discontinuing PEEP. Extrapolation of data on pulmonary capillary wedge pressure to infer quantitative correlations with transmural pulmonary vascular pressures or left ventricular end-diastolic volume should be done cautiously because of the uncertainties introduced by PEEP.

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THE GASPING SYNDROME AND BENZYL ALCOHOL POISONING

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BENZYL alcohol is commonly used as an antibacterial agent in a variety of formulations, including bacteriostatic sodium chloride and bacteriostatic water, that are intended for intravenous administration. Although benzyl alcohol toxicity has been recognized, the concentration that is necessary for antibacterial action appears to be much lower than the concentration that would be dangerous to adults.[1,2] Little, if anything, is known about the possible toxic effects of benzyl alcohol in neonates.

Ten premature infants in our neonatal intensive-care unit developed similar clinical syndromes characterized by the deterioration of multiple organ systems and eventual death, which we believe were the result of benzyl alcohol poisoning. In a preliminary report we have referred to this clinical pattern as the "gasping syndrome."[3] All the infants had originally presented with respiratory distress requiring mechanical ventilation and umbilical arterial catheterization for frequent

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blood gas analysis. They received multiple injections of heparinized bacteriostatic sodium chloride for flushing the catheters, and medications reconstituted with bacteriostatic water, both containing 0.9 per cent benzyl alcohol. The infants then followed a typical course: gradual neurologic deterioration, severe metabolic acidosis, the striking onset of gasping respiration, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, and cardiovascular collapse. Extensive workup and post-mortem findings failed to reveal any recognized cause.

Infants with the gasping syndrome received average daily quantities of benzyl alcohol, in the form of bacteriostatic sodium chloride and bacteriostatic water, of 99 to 234 mg per kilogram of body weight before the onset of gasping. A matched control group, consisting of eight infants who received solutions containing benzyl alcohol as a preservative but did not have the gasping syndrome, received average daily quantities of benzyl alcohol of 27 to 99 mg per kilogram over the same period.

Analysis of blood samples available for six of the infants with gasping syndrome showed levels of benzyl alcohol ranging from 0.610 to 1.378 mmol per liter. Although samples were not available from the matched control group, serums from five comparable control infants who were cared for in our neonatal intensive-care unit after the bacteriostatic preparations were no longer in use were found to contain no benzyl alcohol.

Urine samples available for five of the infants with gasping syndrome were found to contain benzoic acid and hippuric acid — breakdown products of benzyl alcohol — in levels ranging from 0.088 to 0.685 mmol per liter and 0.854 to 2.121 mmol per liter, respectively. Levels of urinary benzoic acid and hippuric acid in the five control infants who did not receive benzyl alcohol were much lower — 0.003 to 0.049 mmol per liter for benzoic acid and 0.60 to 1.060 mmol per liter for hippuric acid.

Since discontinuing the use of bacteriostatic sodium chloride and bacteriostatic water in our nurseries in June 1981, we have seen no further cases of the gasping syndrome. Our experience suggests that the inclusion of benzyl alcohol in drugs and parenteral solutions used in the treatment of sick neonates needs to be reassessed.

Methods

Infants with Gasping Syndrome

Ten neonates who were admitted to the neonatal intensive-care unit over a 20-month period acquired the gasping syndrome. All the infants were of low birth weight and were premature (Table 1). Their birth weights ranged from 620 to 2125 g, with a mean of 1112 g. Their gestational ages ranged from 26 to 34 weeks, with a mean of 29 weeks. Each of the babies had either respiratory distress or apneic spells requiring mechanical ventilation and umbilical arterial catheterization.

Frequent blood sampling was required for blood gas and chemical analyses. The infants received multiple injections of heparinized bacteriostatic sodium chloride to flush indwelling catheters and to initiate peripheral intravenous infusions. In addition, they received multiple medications — including antibiotics, sodium bicarbonate, and calcium — that were reconstituted or diluted with bacteriostatic water.

Table 1. Clinical Data on Ten Infants with the Gasping Syndrome and Eight Matched Control Infants.

Infants with Gasping Syndrome			Matched Control Infants		
Case No.	Birth Weight	Gestational Age	Control No.	Birth Weight	Gestational Age
	g	wk		g	wk
1	620	26	*	*	*
2	800	26	*	*	*
3	830	28	3	720	29
4	900	27	4	1060	29
5	900	29	5	1080	29
6	980	28	6	920	29
7	1220	30	7	1040	30
8	1380	30	8	1360	29
9	1420	32	9	1480	32
10	2126	34	10	1980	34
Means	1112	29		1205	30

*No suitable matched control was available.

During the initial part of hospitalization, the infants' symptoms were easily explained by their underlying illnesses. However, over a period of time they had a similar course of central-nervous-system dysfunction, with hypoactivity, hypotonia, and depression of the sensorium, followed later by apnea, seizure activity, and coma. CT scans were obtained in eight infants. Intracranial hemorrhage (Grades II to IV) was documented in seven cases. One of the infants had no evidence of intracranial bleeding on four separate CT scans. Eight of the infants had electroencephalograms that demonstrated very low voltage and severely abnormal electrical activity. Two of these infants had previously had normal electroencephalograms.

In each case the central-nervous-system deterioration was accompanied by severe metabolic acidosis. Blood pH levels dropped to below 7.25, with base deficits greater than 5 and partial pressures of carbon dioxide in the normal range of 35 to 45 mm Hg. The acidosis persisted in all cases until the time of death, despite infusions of sodium bicarbonate. Serum sodium and potassium were within normal limits in most cases until the onset of renal failure, which occurred later.

The infants had marked skin breakdown and hematologic and hepatic disturbances, including thrombocytopenia, leukopenia, direct hyperbilirubinemia, and hyperammonemia, which failed to respond to repeated transfusions of platelets and blood products. Double-volume exchange transfusions were performed in three cases but did not alter the overall course. All the infants were treated with antibiotics; however, cultures repeated on numerous occasions throughout hospitalization failed to identify sepsis or meningitis.

The day of onset of symptoms varied among the infants. The most striking feature of the syndrome was the presence of gasping respiration, characterized by unremitting gasps that occurred continuously at a rate of approximately 20 per minute, despite high ventilatory settings. The gasping lasted for several hours to a week. The onset of gasping occurred between the ages of 2 and 28 days (Table 2).

During the last several days of life the infants had hypotension and renal failure, which did not respond to dopamine infusions. Cardiovascular collapse and death occurred at 6 to 46 days of age (Table 2).

Control Infants

To compare infants with gasping syndrome with other equally sick neonates who received benzyl alcohol but did not acquire the syndrome, we selected a matched control group from among infants hospitalized during the same 20-month period. All control infants

Table 2. Intake of Benzyl Alcohol, Age at Onset of Gasping, and Age at Death.*

Infants with Gasping Syndrome			Age at Onset of Gasping (days)	Age at Death (days)	Matched Control Infants		
Case No.	Average Daily Intake of 0.9% Benzyl Alcohol Before Onset of Gasping				Control No.	Average Daily Intake of 0.9% Benzyl Alcohol over Same Period as Matched Infant with Gasping Syndrome	
	ml/kg/day	mg of benzyl alcohol/kg/day				ml/kg/day	mg of benzyl alcohol/kg/day
1†	16	144	16	22	§	§	§
2†	26	234	2	19	§	§	§
3‡	14	126	28	31	3	4	36
4	18	162	9	11	4	6	54
5	17	153	19	23	5	3	27
6	23	207	5	12	6	10	90
7	19	171	3	6	7	11	99
8†	15	135	9	23	8	5	45
9†	12	108	7	14	9	8	72
10†	11	99	13	46	10	4	36
Means	17	153	11	21		6	54

*Ten infants received from 11 to 26 ml of benzyl alcohol per kilogram as a 0.9 per cent solution. This provided from 101 to 236 mg of benzyl alcohol per kilogram of body weight. Eight matched control infants received from 3 to 11 ml per kilogram of 0.9 per cent solution, or 29 to 97 mg of benzyl alcohol per kilogram of body weight.

†Both blood and urine specimens were available.

‡Only a blood specimen was available.

§No suitable matched control was available.

required mechanical ventilation and umbilical arterial catheterization. The controls were matched to the infants with gasping syndrome on the basis of birth weight (within 200 g), gestational age (within two weeks), survival beyond three days of life, and similar initial clinical features. The infants who met these criteria and were admitted to our neonatal intensive-care unit nearest the times of admission of the corresponding infants with gasping syndrome were selected for study.

Appropriate matched controls could be found for 8 of the 10 infants with gasping syndrome. Birth weights for the control group ranged from 720 to 1980 g, with a mean of 1205 g. Gestational ages ranged from 29 to 34 weeks, with a mean of 30 weeks (Table 1).

Five additional premature low-birth-weight infants who were hospitalized in the neonatal intensive-care unit after we had stopped using bacteriostatic sodium chloride and bacteriostatic water and who were receiving mechanical ventilation and had umbilical arterial catheters in place were selected at random for blood and urine studies.

Determination of Benzyl Alcohol Intake

Charts of infants with gasping syndrome were reviewed, and the mean daily intake of benzyl alcohol before the onset of gasping was calculated for each, on the basis of the total volume of catheter flushes and medications recorded in the daily intake sheet. Charts were similarly reviewed for the matched control infants. The approximate mean daily intake of benzyl alcohol for each control infant before the onset of gasping in the matched infant with gasping syndrome was calculated. Statistical analysis was by Student's t-test.

Measurement of Benzyl Alcohol and Its Metabolites in Blood and Urine

Blood and urine samples were collected from infants with gasping syndrome within several hours after the onset of gasping and were refrigerated until the time of analysis. Samples were collected in the same manner from the unexposed infants. Levels of benzyl alcohol and benzoic acid in the blood and urine were determined by gas chromatography and confirmed by mass spectroscopic analysis. Levels of hippuric acid in the urine were determined by high-pressure liquid chromatography.

Results

The calculated average daily volume of 0.9 per cent benzyl alcohol received by infants with gasping syndrome before the onset of gasping ranged from 11 to 26 ml per kilogram per day, with a mean of 17 ml per kilogram per day (Table 2). These volumes delivered from 99 to 234 mg of benzyl alcohol per kilogram per day, with a mean (±S.E.M.) of 153±13 mg per kilogram per day. The calculated average daily volume of 0.9 per cent benzyl alcohol received by the matched control infants over the corresponding number of days ranged from 3 to 11 ml per kilogram per day, with a mean of 6 ml per kilogram per day (Table 2). These volumes represent from 29 to 97 mg of benzyl alcohol per kilogram per day, with a mean (±S.E.M.) of 54±9 mg per kilogram per day ($P<0.001$ compared with infants with gasping syndrome).

Concentrations of benzyl alcohol were monitored in serum obtained from six infants with gasping syndrome. A mean concentration (±S.E.M.) of 1.01±0.13 mmol of benzyl alcohol per liter was found (Table 3). No benzyl alcohol was found in the serum of the five infants who had not received bacteriostatic sodium chloride or bacteriostatic water. Although urine from both groups was also analyzed for benzyl alcohol, none was detected.

Urine samples were also monitored for both benzoic acid (the oxidation product of benzyl alcohol) and hippuric acid (the glycine conjugate of benzoic acid). Whereas only trace amounts of benzoic acid (0.029±0.009 mmol per liter) were found in the urine of the five unexposed infants, a significantly higher concentration ($P<0.001$) was found in the urine of five infants with the gasping syndrome (0.377±0.119 mmol per liter) (Table 3).

Levels of hippuric acid in the urine of five infants with gasping syndrome ranged from 0.854 to 2.121 mmol per liter, with a mean value of 1.469±0.25 mmol per liter. Levels in five neonates who were not exposed to benzyl-alcohol preparations ranged from 0.060 to 1.060 mmol per liter, with a mean level of 0.765±0.089 mmol per liter. Levels for the infants with gasping syndrome were significantly higher ($P<0.001$) (Table 3).

Discussion

This study shows that premature infants who received intravenous preparations containing benzyl alcohol as a preservative accumulated benzyl alcohol in their blood. The accumulation was probably due to the large doses of benzyl alcohol relative to the size of the patients, to the reduced capacity of the in-

fants' metabolic systems to detoxify benzyl alcohol, or to both.

The first possibility becomes apparent when one realizes that the single dose of 0.9 per cent benzyl alcohol that is considered safe for healthy human adults is 30 ml[1] —in the range of 0.5 ml per kilogram. In the present study, the babies received 20 to 50 times this amount on a daily basis. Dosages in the same order of magnitude as those have been shown to be lethal in animal studies.[4] In these studies, the median lethal dose for benzyl alcohol in rats was 314 mg per kilogram intravenously and 410 mg per kilogram intra-arterially. This exposure becomes even more critical when one considers that premature infants obviously have a reduced ability to detoxify benzyl alcohol.[4]

Table 3. Levels of Serum Benzyl Alcohol, Urinary Benzoic Acid, and Urinary Hippuric Acid in Infants with the Gasping Syndrome and in Unexposed Infants.*

Group	No. of Infants	Serum	No. of Infants	Urine	
		Benzyl alcohol		Benzoic acid	Hippuric acid
		mmol/liter		mmol/liter	mmol/liter
Unexposed infants †	5	0	5	0.029±0.009	0.765±0.089
Infants with gasping syndrome	6	1.01±0.13	5	0.377±0.119 ‡	1.469±0.251 ‡

*Values expressed as means ±S.E.M.

†Premature infants admitted to the neonatal intensive-care unit after discontinuation of the use of buchweizenic sodium chloride and bacteriostatic water.

‡Significantly different from control ($P<0.001$).

Benzyl alcohol is an aromatic alcohol that is oxidized to benzoic acid, conjugated in the liver with glycine, and excreted in the urine as hippuric acid.[5] Numerous reports have shown that the oxidative processes and conjugation reactions required for the metabolism of such foreign compounds as benzyl alcohol are diminished in the premature infant.[6] This diminution, combined with the very large doses of benzyl alcohol that were administered to these babies, would result in an accumulation of benzyl alcohol in the blood. Such an accumulation may be responsible for the common findings in the gasping syndrome.

Several articles concerning potential multisystem toxic effects of benzyl alcohol similar to the ones in our patients appeared in the literature in the early 1900s. In 1918 Macht described a broad spectrum of complications, including cardiovascular, neurologic, smooth-muscle, and respiratory effects.[7,8] Gruber reported cardiovascular and respiratory toxicity from benzyl alcohol.[9]

In these early animal studies, it was determined that the cardiovascular effects of benzyl alcohol were peripheral in nature, acting at the level of arterial smooth muscle to produce vasodilation and hypotension. Other effects included respiratory stimulation with low doses of benzyl alcohol and respiratory failure at higher doses. Central-nervous-system symptoms were also described and ranged from sedation at low doses to convulsions and paralysis at higher doses.[7]

The neurologic symptoms seen in the present study — including hypoactivity, hypotonia, coma, and seizure activity — may have been due to a direct toxic effect of benzyl alcohol on the central nervous system. The presence of intracranial hemorrhage in seven of the infants failed to explain their unusual neurologic symptoms and electroencephalographic findings. This group of infants reflected the usual frequency and severity of intracranial hemorrhage in the low-birth-weight population.[10] However, of the seven control infants in this study who had CT scans, only one was found to have an intracranial hemorrhage. Gasping, the most striking feature of the syndrome, and apnea may be the results of stimulation of specific respiratory centers. Gasping or apneustic breathing can be caused by injury to the apneustic center of the brain stem located in the pons.[11] Injury at the level of the lower medulla leads to complete apnea. We postulate that benzyl alcohol or one of its metabolites may produce apnea and gasping by exerting direct toxic effects at these respiratory centers.

The metabolic acidosis in these babies may have resulted from accumulation of benzoic acid in the blood. The more than 12-fold increase in benzoic acid in the urine of infants with gasping syndrome, as compared with the controls, was probably a reflection of enhanced conversion of benzyl alcohol to benzoic acid, which at some point must increase blood levels of benzoic acid.

Cardiovascular effects were observed in all the infants with gasping syndrome and produced hypotension, cardiovascular collapse, and death. The hematologic findings included anemia, thrombocytopenia, and leukopenia. These findings suggest the possibility of a benzyl alcohol-induced bone-marrow depression. Hemolytic effects of benzyl alcohol have previously been suggested.[12] Direct hyperbilirubinemia occurred, perhaps as a result of hepatic impairment. It should be pointed out that benzoate is known to displace bilirubin from albumin-binding sites, possibly enhancing the toxicity of bilirubin.[13]

The control infants in this study were initially as sick as the infants with the gasping syndrome, but they did not acquire the gasping syndrome. We postulate that this was because they received much smaller amounts of benzyl alcohol. For various reasons their umbilical arterial catheters were discontinued within the first week of life. They continued to receive benzyl alcohol in the form of flushes for intravenous infusions and diluents for medications. However, the quantities were much smaller than those involved in flushing indwelling catheters used for frequent blood gas sampling. These infants did not have the striking features of the gasping syndrome. It is possible that they did have less severe forms of benzyl alcohol toxicity that were not recognized.

In comparing the time to onset of gasping in selected infants with gasping syndrome with daily dosages of 0.9 per cent benzyl alcohol, a significant correlation coefficient of -0.83 was determined ($P<0.05$). This suggests a definite relation between the intake of benzyl alcohol and the time to onset of gasping.

In June 1981 we stopped using bacteriostatic sodium chloride and bacteriostatic water in our nurseries. Since then, no further cases of the gasping syndrome have occurred. There has been no increase in the incidence of sepsis or meningitis since the use of these bacteriostatic preparations was discontinued.

The clinical features of the gasping syndrome, the relatively large quantities of benzyl alcohol received by these infants, the positive identification of benzyl alcohol and its metabolites in their body fluids, and the known toxic effects of this bacteriostat suggest that benzyl alcohol was involved in the development of the gasping syndrome.

In our view, the addition of benzyl alcohol to preparations given to infants must be reassessed. This reassessment should include an evaluation of the toxicity of the benzyl alcohol contained in individual preparations and of the cumulative quantities of benzyl alcohol that might be received by an infant treated with several preparations.

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CAROTID BRUIT AND THE RISK OF STROKE IN ELECTIVE SURGERY

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THE finding of a carotid-artery bruit before elective surgery leads to a variety of actions among different physicians. Some recommend angiography or noninvasive carotid-artery studies followed by endarterectomy if appropriate,[1,2] others recommend study only in candidates for cardiac bypass surgery[3-5] or operations anticipated to involve large blood losses, and many consider the bruit to be an unimportant risk factor for perioperative or intraoperative stroke.[6-10] However, studies failing to demonstrate a risk of stroke in association with a carotid bruit have been retrospective, with an uncertain true incidence of bruit and stroke,[6-8] and sample sizes in prospective studies[9,10] have not been large enough to demonstrate that a carotid bruit does not represent a risk for stroke.

In this study, we prospectively examined 735 unselected patients undergoing elective surgery, to determine the incidence of carotid bruit and postoperative stroke. We found that of 104 patients (14 per cent) who had bruits, only one had a stroke within three days postoperatively. Of the 631 patients without a bruit, four had a stroke within three days after operation. The overall incidence of stroke was 0.7 per cent and was not different in patients with and without bruits. All the strokes occurred in patients undergoing coronary bypass procedures and were thought to be embolic in nature.

Methods

Patient Population and Data Acquisition

All patients over the age of 55 who were scheduled for non-neurologic elective surgery at the Massachusetts General Hospital from Tuesdays through Fridays during a nine-month period were identified from daily listings in the anesthesia department. One of three neurologists located all patients who were available for examination on the day before surgery.

The responses to seven standardized questions were recorded on a coded form to determine whether there was a history of transient monocular blindness, transient ischemic attack, stroke, myocardial infarction, or endarterectomy. Questions concerning transient monocular blindness and transient ischemic attack were asked twice. Auscultation of the carotid arteries was performed in a uniform manner using a stethoscope bell in a quiet environment with the patient reclining, his neck extended 30 degrees and his breath held in inspiration. The pitch (high or low) and duration (long or short, systolic or diastolic) of bruits were recorded. If a bruit was detected, the anterior thorax was examined for basal heart murmurs, and the proximal carotid arteries were palpated in order to determine whether the sound was radiated. Seventy-two per cent of the patients with bruits were examined by a second neurologist who had knowledge of the bruit, with agreement that the bruit was focal and not radiated in all but one case. Three to five days after the operation, patients were examined to determine whether a stroke had occurred. Postoperative stroke was defined as occurring in the

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Information of Importance To Physicians and Other Health Professionals

reviewed the data in these studies and issued a statement in the June 1982 issue of *Pediatrics*, advising that the use of salicylates should be avoided in children suffering from influenza or varicella.

The committee recommended "that consideration should be given to the advisability of using any antipyretic medications for these illnesses."

Because of a number of criticisms of the conduct of these studies and the interpretation of the data, FDA undertook an independent analysis of the matter. This analysis included: (1) a review of materials available from the investigators in Arizona, Michigan, and Ohio; (2) a review of summaries provided by CDC on studies concerning RS and salicylates; (3) a review of analyses by employees and consultants of manufacturers of salicylate drug products and consumer representatives; (4) site visits to the Michigan and Ohio state health departments to obtain further details on how these studies were conducted and to audit data on case records; and (5) a review of a subset of the data from the Ohio study containing day-by-day information on disease symptoms and drug use.

In the course of the review, questions were raised about study design; however, these were not considered sufficient to change substantially the interpretation of the data. The FDA analysis generally supported the association between salicylates and RS shown in the earlier evaluations of the data.

The studies performed are not able to demonstrate conclusively whether the association is causal, but the accumulated evidence is sufficiently strong to justify the FDA's advisory caution on the use of salicylates in children with those viral illnesses particularly associated with the development of RS.

FDA presented its analyses at an open public meeting on May 24, 1982, which it sponsored jointly with CDC and the National Institutes of Health (NIH). At the completion of the meeting, the majority of the scientific experts believed that the new analyses supported the earlier evidence suggesting an association between use of salicylates and the development of RS.

Aspirin and other salicylates are found in single ingredient products or in combination with other medicines; labels of over-the-counter drug products contain a list of ingredients. Aspirin remains a medically useful drug with anti-inflammatory actions not found in other over-the-counter antipyretics.

Benzyl Alcohol May Be Toxic to Newborns

Solutions containing benzyl alcohol or other preservatives should not be used in newborns to flush intravascular catheters. Solutions for diluting or reconstituting medications for newborns also should contain no benzyl alcohol or other preservatives.

FDA has received reports of 16 fatalities in newborns weighing less than 2,500 grams in whom bacteriostatic sodium chloride for injection containing 0.9 percent benzyl alcohol had been used for flushing intravenous catheters.[1,2] Some of the infants received additional benzyl alcohol when bacteriostatic water was used to dilute or reconstitute medications.

The deaths were preceded by a syndrome consisting of metabolic acidosis, central nervous system depression, respiratory distress progressing to gasping respirations, hypotension, renal failure and sometimes seizures and intracranial hemorrhages. Blood and urine samples of affected infants revealed high levels of benzyl alcohol, benzoic acid or its metabolite, hippuric acid.

Toxicity from benzyl alcohol appears to have been caused by large daily doses of benzyl alcohol per kilogram of body weight; daily intake in these cases ranged from 99–404 mg/kg/day. Each milliliter of 0.9 percent solution contains 9.0 mg of benzyl alcohol.

In the two medical centers reporting the 16 cases, no additional cases of the toxic syndrome were seen after solutions containing benzyl alcohol were eliminated.[1,2] There have been no reports of toxicity in older infants, children, and adults.

On May 28, FDA sent letters to pediatricians, hospital pharmacists, and hospital administrators, recommending that solutions used to flush intravascular catheters or for diluting or reconstituting medications in newborns not contain benzyl alcohol or any other preservative. Sterile sodium chloride for injection (not bacteriostatic sodium chloride for injection) should be used for flushing intravenous catheters.

The agency is working on labeling changes with the manufacturers and the U.S. Pharmacopoeia for the practitioner insert and the containers of sodium chloride and water containing benzyl alcohol.

Caution must be used in attributing illness or death to benzyl alcohol in individual babies; many of the clinical features ascribed to benzyl alcohol toxicity are found in newborns seriously ill from other causes. The babies described with benzyl alcohol toxicity had serious underlying disease, but they also had biochemical evidence of benzyl alcohol toxicity.

FDA is involved in gathering more data on the problem, in cooperation with the Armed Forces Institute of Pathology, neonatologists, and the U.S. Centers for Disease Control (CDC).

Collaborative efforts with drug manufacturers, the American Society of Hospital Pharmacists, the American Academy of Pediatrics, the American Nursing Association, the U.S. Pharmacopoeial Convention, CDC[3], and others are under way to insure that the health care community is fully informed of the recent information.

Physicians can assist in this effort by using the form on the back of this *Drug Bulletin* to report any possible or definite cases of toxicity associated with benzyl alcohol.

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Hepatotoxic Potential of Ketoconazole Under Investigation

Three cases of fatal, massive hepatic necrosis, one case of nonfatal hepatitis and necrosis, and 20 cases of liver injury (usually with jaundice) have been reported in patients taking ketoconazole (Nizoral).

The drug is the only oral therapy approved for systemic fungal infections and is valuable for serious, systemic infections. (See November 1981 *Drug Bulletin.*)

Several cases of hepatitis were reported in the literature[1-3] just prior to and shortly after the drug's approval in June 1981. In these cases jaundice cleared and liver enzyme levels returned to normal after treatment was stopped or, in one case,[3] with continued ketoconazole treatment.

The three reported deaths occurred despite discontinuation of ketoconazole. The first occurred in a 67-year-old woman on ketoconazole therapy for 8 weeks. The second occurred in a 64-year-old man taking the drug for 28 days who had major surgery despite abnormal liver function and subsequently died of sepsis. The third case was a 22-year-old woman on ketoconazole therapy for 6 days. This patient was being treated for leukemia with drugs of known hepatotoxic potential.[4]

Although these cases were confounded by medical history and concomitant or preceding treatment with other drugs, the similar sequence and pattern of liver function abnormalities suggest that ketoconazole also played a role.

In the nonfatal case of hepatic necrosis, the 75-year-old female patient had been on ketoconazole therapy for 3 months with no concomitant medication.[4]

Manufacturer Sends Letter

Upon learning of the first case of fatal hepatitis that developed during ketoconazole therapy, the manufacturer, Janssen Pharmaceutica, sent a letter in March 1982 to prescribers informing them of the possibility of hepatotoxicity and alerting them to the consequent additions to the labeling.

The following was added to the Warnings section of the package insert for ketoconazole:

> Several cases of possible idiosyncratic hepatocellular dysfunction have been reported during NIZORAL treatment. It is important to recognize that liver disorders may occur with NIZORAL therapy. The rare occurrences of liver disorders could be potentially fatal unless properly recognized and managed. It is desirable to perform liver function tests, such as SGGT, alkaline-phosphatase, SGPT, SGOT and bilirubin, before treatment and at periodic intervals during treatment (monthly or more frequent), particularly in patients who will be on prolonged therapy or who have a history of liver disease. Instances of minor elevations of liver enzyme levels in patients on NIZORAL have been shown to normalize during therapy and may not necessitate discontinuation of treatment. However, if liver function tests are significantly elevated or other signs and symptoms are suggestive of hepatocellular dysfunction, ketoconazole should be discontinued.

The following has been added to the Precautions section:

> Information for Patient: Patient should be instructed to report any signs and symptoms which may suggest liver dysfunction so that appropriate bio-chemical testing can be done. Such signs and symptoms may include unusual fatigue, nausea or vomiting, jaundice, dark urine or pale stools.

Additional Cases

In addition to the four cases discussed previously, FDA has received reports of 20 additional cases of other liver injury, signs and symptoms of which included jaundice, elevated transaminases, bilirubin and alkaline phosphatase, anorexia, nausea, and/or

Reye Syndrome — Continued

munity, the drug industry, and consumer organizations. It was the consensus of the scientific working group at the completion of the meeting that the new analysis supported the earlier evidence of an association between salicylates and Reye syndrome.

As a result of this entire review process, the Surgeon General advises against the use of salicylates and salicylate-containing medications for children with influenza and chickenpox.*

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*The Surgeon General notes that the FDA will notify health professionals through its *Drug Bulletin*, will develop lay-language information for widespread distribution, and will take the steps necessary to establish new labeling requirements for drugs containing salicylates.

Epidemiologic Notes and Reports

Neonatal Deaths Associated With Use Of Benzyl Alcohol — United States

Sixteen neonatal deaths thought to be caused by the benzyl alcohol preservative used in some intravascular solutions have been reported to the Food and Drug Administration (FDA) by 2 medical centers (1,2). The deaths occurred in pre-term neonates weighing <2500 gms who had central intravascular catheters flushed periodically each day with bacteriostatic normal saline containing 9 mg/ml benzyl alcohol. Ten deaths occurred in 1 institution over a 6-month period and 6 deaths occurred in the other institution over a 16-month period. Investigators in the 2 hospitals have reported that similar deaths have not occurred since flush solutions without preservatives have been substituted for those with the benzyl alcohol.

Onset of toxic illness in the infants occurred between several days and a few weeks of age with a characteristic clinical picture that included metabolic acidosis progressing to respiratory distress and gasping respirations. Many infants also had central-nervous-system dysfunction, including convulsions and intracranial hemorrhage; hypotension leading to cardiovascular collapse was a late finding usually presaging death.

Gas chromatographic analysis demonstrated benzyl alcohol or its metabolites in blood and urine samples from infants in 1 hospital. Retrospective analysis of urine samples from 5 infants in the other hospital for organic acid profile by gas-liquid chromatography showed urine benzoate levels of 4.4-16.1 mg/mg creatinine and hippurate levels of 7.4-33.3 mg/mg creatinine (normal values = 0-trace); serum benzoic acid levels were 8.4-28.7 mEq/L (normal = 0). Review of the medical records of the affected infants resulted in estimates of daily intake of benzyl alcohol ranging from 99 to 405 mg/kg/day.

Based on these reports, the FDA has recommended that intravascular flush solutions containing benzyl alcohol not be used for newborns and that diluents with this preservative not be used as medications for these infants.

Illness suspected of having been caused by use of benzyl alcohol should be reported promptly to the FDA, Division of Drug Experience, Attn: Judith K. Jones, M.D., Ph.D., Room 15-B-07, HFD-210, 5600 Fishers Lane, Rockville, Maryland 20857; telephone (301)443-4580.

Reported by JJ Gershanik, B Beecher, W George, A Sola, M Leither, C Kapadious, Southern Baptist Hospital, New Orleans, Louisiana; WJ Brown, NRM Burst, HTC Gipson, RK Huston, NG Kennaway, Oregon Health Sciences University, Portland; Div of Drug Experience, Office of Biometrics and Epidemiology, Bureau of Drugs and Biologics, FDA; Chronic Disease Div, Center for Environmental Health, Hospital Infections Program, Center for Infectious Diseases, CDC.

Neonatal Deaths — Continued

Editorial Note: Benzyl alcohol is an aromatic alcohol usually used in a concentration of 0.9% as a bacteriostatic preservative in multiple-dose vials of solutions or drugs for parenteral therapy. Bacteriostatic sodium chloride, USP, is frequently used in the management of critically ill patients to flush intravascular catheters after the addition of medications or the withdrawal of blood; and sterile bacteriostatic water for injection, USP, is used to dilute or reconstitute medications for intravenous use. In addition, medications, such as some formulations of sodium heparin, USP, that are frequently used for infants and other critically ill patients may be preserved with benzyl alcohol.

Toxic effects of benzyl alcohol, including respiratory failure, vasodilation, hypotension, convulsions, and paralysis have been known for years (3-5). However, little is known about the toxic effects or levels of benzyl alcohol in neonates, especially in sick premature infants. Animal toxicity studies (6) show an LD_{50} of approximately 33 ml/kg (300 mg/kg) in rats treated by rapid intravenous infusion with 0.9% benzyl alcohol, although 40 ml/kg (360 mg/kg) by slow intravenous infusion was tolerated without mortality. Adult dogs were killed by doses of 88-113 ml/kg (830-1060 mg/kg) of 0.9% benzyl alcohol intravenously, but tolerated smaller infusions without signs of toxicity. The serum half-life of benzyl alcohol in adult dogs is estimated at 1.5 hours. On the basis of the animal studies, it has been estimated that rapid intravenous infusion of adult humans with as much as 30 ml of 0.9% benzyl alcohol (approximately 4.5 mg/kg) in saline should be safe (6).

Benzyl alcohol is normally oxidized rapidly to benzoic acid, conjugated with glycine in the liver, and excreted as hippuric acid. However, this metabolic pathway may not be well developed in premature infants. The benzyl alcohol may therefore have been metabolized to benzoic acid, which could not be conjugated by the immature liver but accumulated, causing metabolic acidosis (2).

These reports of neonatal toxicity from benzyl alcohol are highly noteworthy. However, caution must be exercised in attributing individual illness to benzyl alcohol since many of the described clinical features commonly occur in neonates seriously ill from other causes. Newborns most likely to receive large volumes of flush solutions, relative to body weight, are the very small, sick premature infants who already have a high risk of mortality. Thus, mortality potentially attributable to benzyl alcohol should also be assessed by a careful comparison of neonatal mortality in newborns receiving large amounts of non-bacteriostatic flush solutions and medications with comparable newborns receiving large amounts of bacteriostatic solutions and medications. Retrospective analyses of newborns who received saline flushes with benzyl alcohol and survived are also needed to establish whether a dose-response relationship exists between clinical and laboratory findings and the intensity of exposures to benzyl alcohol, and to identify more completely the pathologic and clinical features of toxicity in newborns.

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Fatal Benzyl Alcohol Poisoning in Neonatal Intensive Care Units

A New Concern for Pediatricians

In May 1982, the Food and Drug Administration urged hospitals and pediatricians to discontinue the use of intravenous (IV) infusions of saline solution containing benzyl alcohol, as well as medications containing benzyl alcohol as a preservative, in premature infants. More than 50,000 letters were mailed to pediatricians, hospital pharmacists, and hospital administrators notifying them of the problem.[1] The FDA based its recommendation on the results of two studies that suggested that benzyl alcohol, used as a preservative in small multiple-dose vials of sodium chloride solution or water for injection, had caused a fatal toxic syndrome in premature infants.

The suspicion that a benzyl alcohol preservative was associated with these neonatal deaths was first raised by Gershanik and associates[2] from the Southern Baptist Hospital, New Orleans, at the January 1982 meeting of the Southern Society for Pediatric Research. Gershanik and his associates described five neonates during a 16-month period of time; all were preterm infants with a gestational age range of 26 to 30 weeks and birth weights ranging from 620 to 1,380 g. All five infants had respiratory difficulty that required mechanical ventilation, placement of umbilical catheters, and frequent blood analyses, and all had demonstrated intracranial hemorrhage. All infants received frequent injections of heparinized sodium chloride solution containing 0.9% benzyl alcohol as "flushes" for IV lines. In addition, medications given to these infants were reconstituted with water that contained benzyl alcohol. The total volume of such solutions that the affected infants received was estimated at 11 to 26 mL/kg/day, with the calculated doses of benzyl alcohol being 99 to 234 mg/kg/day.

The syndrome ("the gasping syndrome") experienced by these five infants included progressive CNS depression and hypoactivity, increasing respiratory distress, severe metabolic acidosis, gasping respiration, thrombocytopenia, hepatic and renal failure, hypotension, and cardiovascular collapse followed by death. At postmortem examination, no cause for death was demonstrable. In each infant, benzyl alcohol was identified in the urine, with concentrations ranging from 50 to more than 200 mg/L. In addition, hip-

Marginal Comments

puric acid, an end product of benzyl alcohol metabolism, was identified in the urine. The use of benzyl alcohol in flushes and in medications was discontinued in this nursery, and no similar cases occurred.

In May 1982, Brown and colleagues[2] from the Emanuel Hospital, Portland, Ore, described 11 infants, all weighing less than 1,250 g, who they believed suffered from benzyl alcohol poisoning. During the six-month period of their study, August 1981 through January 1982, ten of 11 infants died. Nine infants were sufficiently ill to require ventilatory support, and all had at least one central venous or arterial catheter. All infants were receiving ampicillin sodium and gentamicin sulfate and standard fluid and electrolyte solutions. Normal saline solution containing 0.9% benzyl alcohol was used during catheter placement to flush the catheters after administration of medication and after blood sampling. The average dose of benzyl alcohol was estimated to be 191 mg/kg/day; one infant received 405 mg/kg/day.

Symptoms usually occurred between the second and fourth day and included progressive obtundation, decreased responsiveness, suppression of the EEG, frequent seizures (eight of ten infants within 24 hours of onset of illness), progressive bradycardia, metabolic acidosis with an average anion gap of 29 mmole/L, hypotension, cardiovascular collapse, and death. Ten of 11 infants were unresponsive to therapy.

Gas-liquid chromatography on urine samples disclosed benzoic acid (an intermediate product of benzyl alcohol metabolism) values of 4.4 to 16.1 mg/mg of creatinine (normally, only a trace is present) and hippuric acid values of 7.4 to 33.9 mg/mg of creatinine (normally, only a trace is present). Serum benzoic acid values in five infants ranged from 8.4 to 28.7 mmole/L (normal, 0 mmole/L); this partially explains the anion gap. In one infant who survived, use of benzyl alcohol was discontinued because of the presence of a large anion gap and a serum benzoic acid level of 14.4 mmole/L, with subsequent full recovery.

Benzyl alcohol is oxidized in the liver to benzoic acid and then conjugated with glycine to form hippuric acid. Kimura and associates[4] have demonstrated that the lethal dose for 50% of rats given 0.9% benzyl alcohol IV as a single dose is 305 to 450 mg/kg. This dose is not too far removed from that given to premature infants during the course of a day in the previously described cases. Furthermore, clinical manifestations produced in animals given toxic doses of benzyl alcohol[3,4] simulate those described in human infants by Gershanik et al[2] and Brown and colleagues.[2] It has been postulated that the quantity of benzoic acid produced may exceed the capacity of the immature liver for detoxification, so that accumulation of benzoic acid occurs with subsequent metabolic acidosis. While the benzyl alcohol in both studies was given on multiple occasions (rather than as a single dose), immaturity of liver enzymes with slowed metabolism of the parent compound (benzyl alcohol) and its metabolite (benzoic acid) could lead over time to accumulation of both compounds. Each seems to be intrinsically toxic at increased serum concentrations. Benzoic acid is thus a plausible explanation for the observed metabolic acidosis and increased anion gap. The cause of neurologic symptoms is not yet clear at this time but is presumably due to the toxicity of benzyl alcohol or one of the metabolites.

While it is clear that Gershanik et al[2] and Brown et al[2] have presented data that are uncontrolled and wanting in some quantitative respects, it seems most appropriate for the FDA to alert pediatricians to the potential risk associated with benzyl alcohol. This is particularly true because there are alternative solutions, such as sodium chloride or water for injection, that contain no benzyl alcohol for flushing IV lines, as well as for reconstituting medications.

Concern might be raised that confounding medical disease (bacteremia and sepsis) may have existed in some of these infants and could conceivably have accounted for their illness. The fact that this syndrome has not occurred, however, after the discontinuation of use of benzyl alcohol in these two nurseries, adds plausibility to the presumed toxicity of the alcohol. Certainly, one would like to have further data concerning the toxic effects of benzyl alcohol, benzoic acid, hippuric acid, and other possible but as yet undetermined metabolic products. In addition, one would like to have data on the rate of accumulation of specific metabolites and on the specific steps in the metabolism of benzyl alcohol that are delayed in the premature liver.

The amount of benzyl alcohol contained in IV medications used in the nursery is small, eg, aminophylline hydrochloride (2%), clindamycin phosphate (0.9%), and heparin sodium (0.1%). The volume of fluid as sodium chloride containing benzyl alcohol, however, is large and is thus a risk for the premature infant. While further studies are being carried out to confirm and clarify the mechanism of toxicity of benzyl alcohol, it is prudent for pediatricians to discontinue the use of solutions that contain benzyl alcohol to flush IV catheters in premature infants. Sterile sodium chloride for injection (not bacteriostatic sodium chloride) should be used instead. Furthermore, reports of possible or definite toxic effects associated with benzyl alcohol should be reported to the FDA. While these solutions have been used in adults for decades with apparent impunity, the present experience serves to reinforce the fact that children and neonates are clearly different than adults as it relates to the handling of drugs.

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LOW-DOSE STEROID REGIMENS AFTER RENAL TRANSPLANTATION

SIR,—We support Professor de Wardener's view (April 24, p. 962) that Professor Morris and colleagues' paper on low-dose prednisone in renal transplantation was ungenerous to other workers and disagree with the Oxford team's reply that the reports of McGeown and colleagues did not have a major impact on practice. The excellent results of the Belfast unit led us, from May, 1978 to May, 1979, to do a prospective controlled trial of low versus high dose steroids in the most active transplant hospital in the U.K. In contrast to the Oxford series our low-dose patients received prednisolone 20 mg daily, as recommended by McGeown,[1] and we did not routinely give intravenous methylprednisolone at the end of the first week. Though we do not suggest that intravenous and oral steroid doses are equivalent, the additional intravenous steroid given by Morris et al. to their low-dose group led to a similar total steroid to that in their high dose group, 11·8 g compared with 11·0 g in the first three months. We reported no difference in graft survival between the high and low dose groups but did find a significantly higher mortality in the high dose group.[2] Since our study was completed, we have routinely used low dose steroid regimens. A further 220 patients have been transplanted with a continued low mortality.

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FATAL BENZYL ALCOHOL POISONING IN A NEONATAL INTENSIVE CARE UNIT

SIR,—Between August, 1981, and January, 1982, sixteen infants weighing <1250 g were admitted to our nursery. Ten of these babies died of a syndrome which we feel was caused by benzyl alcohol poisoning. One infant with the biochemical hallmarks of this syndrome recovered after benzyl alcohol was removed from his intravenous fluids. The purpose of this letter is to alert clinicians to what appears to be a major cause of neonatal morbidity and death. A more detailed report is in preparation.

Of the ten infants whom we recognised as having developed the syndrome, nine were ventilator dependent and all had at least one central catheter. All infants were receiving ampicillin and gentamicin and standard fluid and electrolyte therapy. Bacteriostatic normal saline containing benzyl alcohol 9 mg/ml was used during catheter placements, to flush the catheters after administration of medication, and after blood sampling.

Although the quantity of saline flush in the ten cases varied, the minimum intake was 14·4 ml/kg/day (130 mg/kg/day of benzyl alcohol); the average volume was at least 21·2 ml/kg/day (191 mg/kg/day); some days the volume of flush was as high as 45 ml/kg (405 mg/kg).

Before the onset of symptoms, usually around the second to fourth day, all the infants developed progressive metabolic acidosis, the average anion gap at that time being 29 mmol/l (normal ×12–18). Slowly progressive bradycardia, often associated with gasping respiration, soon followed. Seizures were frequent (eight cases out of ten) and usually developed within 24 h. The infants became gradually more unresponsive with very depressed EEGs, and eventually they had only reflex movements or occasional gasping respiration. Hypotension leading to cardiovascular collapse was a late finding, usually presaging death. Intracranial haemorrhage was present in six cases (grade I in five, grade III in one).

The clinical picture was therefore that of an infant with a severe metabolic acidosis who was unresponsive to treatment and whose symptoms resembled those of a progressive encephalopathy.

The clue to the cause of the acidosis came from examination of the urinary organic acid profile by gas-liquid chromatography. All samples contained huge quantities of benzoic and hippuric acid. Retrospective analyses of urine which had been saved frozen from five infants revealed urinary benzoate values of 4·4–16·1 mg/mg creatinine (normal a trace at most) and urinary hippurate values of 7·4–33·9 mg/mg creatinine (normal a trace at most). Serum benzoic acid values have been measured on five of the infants; values range from 8·4 to 28·7 mmol/l (normal zero). Thus, at least in these infants, the benzoic acid accounts for much of the unexplained anion gap.

The one infant who survived acquired metabolic acidosis by 36 h of age. At that time the anion gap was 36 and the serum benzoic acid 14·4 mmol/l. Within four days of withdrawal of the benzyl alcohol, the biochemical values had returned to normal.

We postulate that the benzyl alcohol is metabolised to benzoic acid which is then converted by the liver to hippuric acid. The quantity of the benzoic acid exceeded the capacity of the immature liver for detoxification so that the benzoic acid accumulated in serum, causing the metabolic acidosis. The cause of the neurological symptoms is not yet clear, but presumably they are due to the toxicity of benzyl alcohol or one of its metabolites.

Since we stopped using bacteriostatic normal saline, five out of six infants weighing <1250 g who have been admitted to our unit have survived. Gershanik et al.[1] have suggested that benzyl alcohol was responsible for at least five deaths in their unit. Our findings, which extend their data considerably, support that conclusion. Until further data are available, we recommend that the use of fluids containing benzyl alcohol be discontinued in the care of small premature infants.

This work supported by grant C-195, March of Dimes Birth Defects Foundation.

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ROBERT K. HUSTON
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ALCOHOL AND THE RULE OF FOUR

SIR,—Your editorial on alcohol disease (May 15, p. 1105) states that the "safe" upper limit of daily consumption is "four pints of beer or four measures of spirits". This is misleading, unless you meant double measures of spirits. Half a pint of beer (285 ml; 3·6 g ethanol per 100 g) is roughly equivalent to one measure of, say, whisky (one-fifth of a gill [28·5 ml; 35 g per 100 g),[2] so the corrected safe upper limit might perhaps be four half-pints or four nips.

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P. LAWFORD

FERTILITY AFTER GONORRHOEAL PELVIC INFLAMMATORY DISEASE

SIR,—In your Feb. 20 editorial on the bacteriology of acute pelvic inflammatory disease (PID) you stated that involuntary infertility was more common after gonococcal than after non-gonococcal PID. The paper cited[3] has been misquoted since it states: "In this study fertility was reduced less by gonorrheal salpingitis than by non-gonorrheal infections."

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Newcastle upon Tyne NE4 6BE

R. S. PATTMAN

*** The above 2 criticisms are just.—ED. L.

1. McGeown MG, Laughridge WGG, Alexander JA, McEvoy J, Kennedy JA, Douglas J, Clarke SD, Heaven JC, Nelson SD. 100 kidney transplants in the Belfast City Hospital. *Lancet* 1977; ii: 648–51.
2. Buckels JAC, Mactaggart P, Barnes AD. Controlled trial of low versus high dose oral steroid therapy in 100 cadaveric renal transplants. *Proc EDTA* 1981; 18: 394–99.
1. Gershanik JJ, Boecler B, George W, et al. The gasping syndrome: Benzyl alcohol (BA) poisoning? *Clin Res* 1981; 29: 694A.
2. Diem K, Lentner C, eds. Geigy scientific tables. 7th rev. Basle: Geigy, 1970: 502.
3. Weström L. Effects of acute pelvic inflammatory disease on fertility. *Am J Obstet Gynecol* 1975; 121: 707–13.

Chapter VIII

Pediatric End-Stage Renal Disease

Key Words:

- Pediatric ESRD
- ESRD incidence in children
- ESRD patient survival in children
- Pediatric dialysis
- Causes of pediatric ESRD
- Renal transplants in children
- CAPD in children
- Hemodialysis in children

Unique characteristics of children and adolescents make it imperative to specifically evaluate their different etiologies of renal failure, treatment, mortality, and overall patient and transplant graft survival. (McEnry; Fine, Salusky, et al 1987; Fine 1987; Ettenger 1987). These factors include development of cognition, secondary sexual characteristics and physical growth. It has also been reported that there are differences in immune responsiveness in children (Ettenger 1987; Parekh 1995) which may account for differences in transplant outcomes. For these reasons, the pediatric ESRD population requires special attention, and this chapter will focus on the incidence, prevalence, and modalities of treatment, survival outcomes and cause specific mortality as related to the national pediatric ESRD population.

The reported upper age cutoff for pediatric patients used among the ESRD registries worldwide ranges between 15 and 19 years. As in earlier Annual Data Reports, this 1998 Annual Data Report defined pediatric as all patients less than or equal to 20 years. In many of the analyses in this chapter, pediatric patients are further divided into 5-year age groups: 0-4, 5-9, 10-14, and 15-19 years.

Several definitions of age are used in this chapter: 1) age is defined as age at onset of ESRD for analyses of incidence and dialysis patient survival; 2) age on December 31 is used for analyses of point prevalence; and 3) age at time of transplantation is used for analyses of kidney transplants. In all cases, only patients less than 20 years of age are considered here.

Incidence of Reported Pediatric ESRD

Pediatric annual incidence counts for the 1995-96 period (1.087) increased compared to the 1993-94 period (928). Last year's report showed a small increase in incidence in 1995. This was thought to be due more to the inclusion of non-Medicare patients in the 1994-95 incident patient counts reported by HCFA rather than an increase in diagnosis and treatment for younger patients with ESRD. Future incident data will need to be collected to ascertain whether there is an actual increase in incidence for pediatric groups.

Table VIII-1

Pediatric ESRD Incidence and Prevalence Counts and Rates, 1994-96

Age at Incidence	Incidence		Point Prevalence*	
	Average Counts Per Year	Unadjusted Annual Rate**	Average Counts Per Year	Unadjusted Annual Rate
0-4	158	9	362	20
5-9	137	8	676	36
10-14	242	14	1,284	70
15-19	523	30	2,455	136
All Pediatric (0-19)	1,060	15	4,777	65
Adults (20-44)	12,032	122	69,374	694

*Table VIII-1. *Alive on December 31 of 1994-96. **Per million ppulation (in each group), adjusted for sex and race. Patients in Puerto Rico and U.S. Territories and cases where race is "other" or "unknown" are excluded. Counts are averaged over a three year period. Includes Medicare and Non-Medicare*

Among both the pediatric and adult ESRD populations, rates of ESRD incidence increase substantially with increasing age. The incidence rate of treated ESRD, adjusted for race and sex, is much higher among adults than among children. During 1996 the adjusted ESRD incidence rate per million United States population (in each age group) was 13 for ages 0-19 years, 117 for ages 20-44 years, 542 for ages 45-64 years, 1144 for ages 65-74 years, and 1079 for ages 75 and over (Reference Table A.6). A higher ESRD incidence rate with older age is also found across the 5-year age groups within the pediatric cohort, when adjusting for differences in sex and race. Table VIII-1 indicates that average incidence rates over the combined years 1994-96 were more than twice as high among children 15-19 years (30 per million) compared to children 10-14 years (14 per million), and more than three times higher than rates for children 0-4 (9 per million) and 5-9 (8 per million) years of age at onset of ESRD. Average annual counts of incident ESRD among children for the years 1994-1996 show that 523 out of the 1060 children newly beginning treatment for ESRD (49 percent) were between the ages of 15 and 19 (Table VIII-1).

Figure VIII-1

Pediatric Treated ESRD Incidence Rates by Race and Age, 1994-96

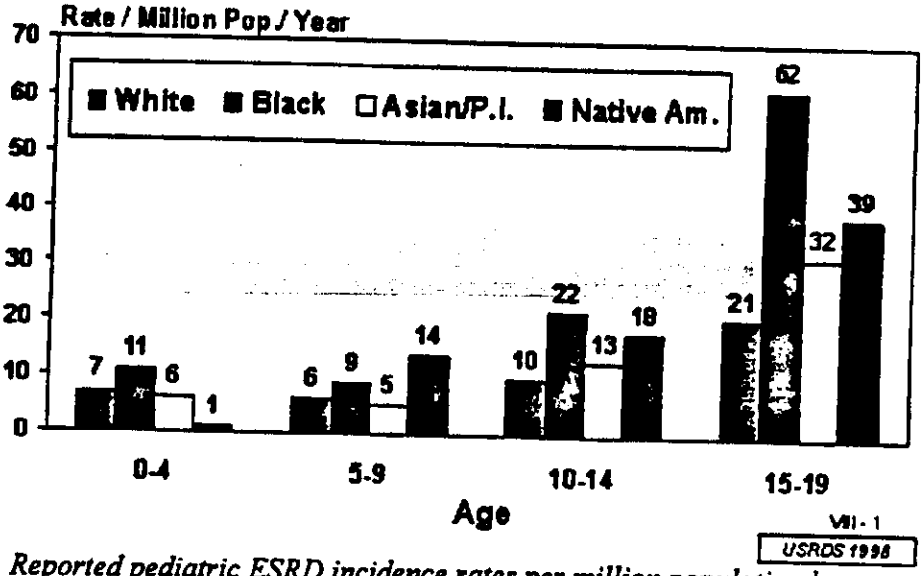


Figure VIII-1. Reported pediatric ESRD incidence rates per million population by age group and race, adjusted for sex. Average rate per year, 1994-96.
Includes all children (ages 0-19 years) adjusted for sex. Patients in Puerto Rico and U.S. Territories and cases where race is "other" or "unknown" are excluded. Medicare and Non-Medicare patients are included. Source: Reference Tables A.8 and A.31

Within the pediatric ESRD population, there are large variations in the incidence rates of ESRD by race, as well as by age. The pediatric treated ESRD incidence rates per million United States population per year for the 1994-96 period were 11 for Whites, 26 for Blacks, 14 for Asians/Pacific Islanders, and 21 for Native Americans. The higher overall incidence of ESRD for Black children was primarily the result of an almost three-fold excess of ESRD, in the 15-19-year-old age group among Blacks compared to Whites (62 per million versus 21 per million). Treated ESRD incidence rates in Whites and Blacks differed less in the younger age groups. The incidence rates for Native Americans show a similar pattern compared to Whites, with a rate of 39 per million in Native Americans between the ages of 15-19, almost twice that of Whites in the same age group.

Figure VIII-2

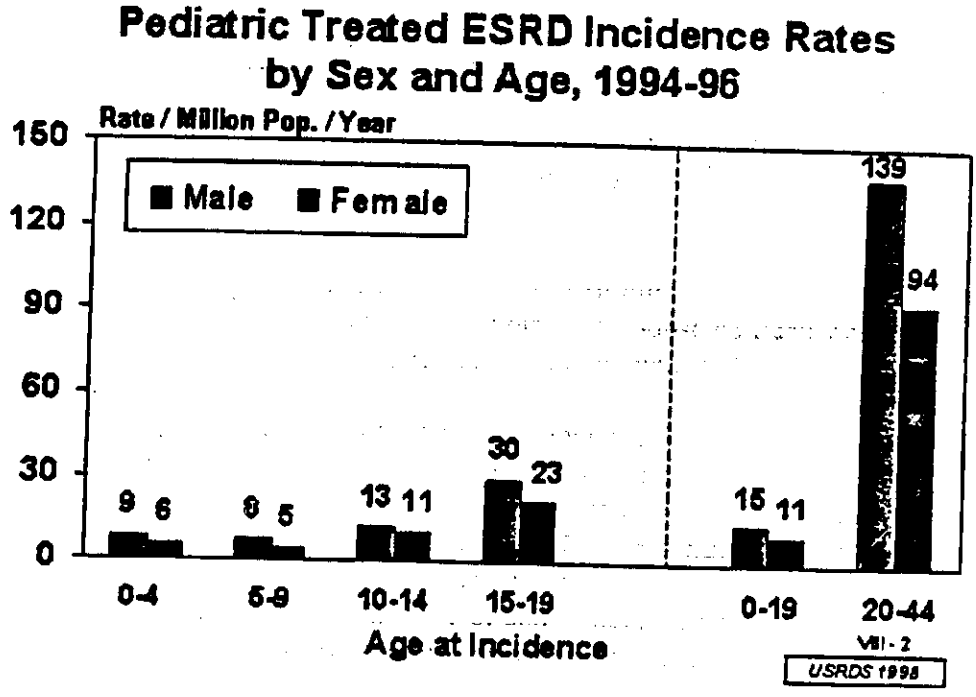


Figure VIII-2. Reported pediatric ESRD incidence per million population by age and sex, adjusted for race. Average rate per year, 1994-96. Incidence rates for children (ages 0-19 years) are adjusted for race. Patients in Puerto Rico and U.S. Territories and cases where race is "other" or "unknown" are excluded. Medicare and Non-Medicare patients are included. Source: Reference Tables A.8 and A.31

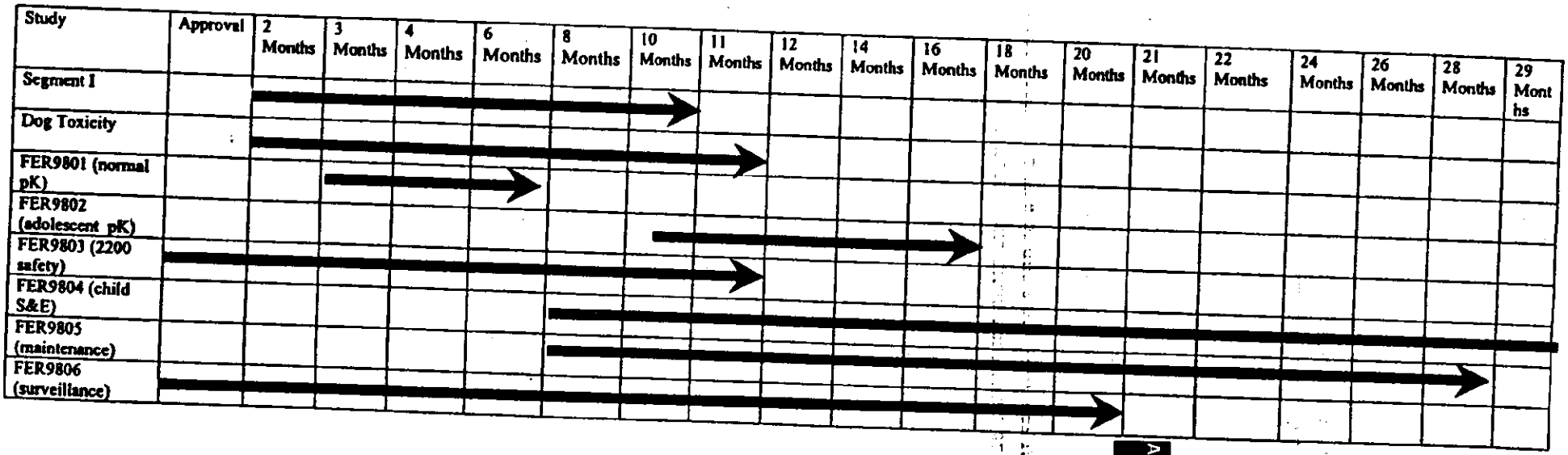
Figure VIII-2 illustrates the incidence of treated ESRD by sex, according to 5-year age groups. Treated incidence rates of ESRD were greater for boys than girls overall. This reflects the higher incidence of congenital disorders including obstructive uropathy and renal dysplasia, which occur more commonly in boys and are the cause of 15 percent of the total incident cases in the pediatric ESRD population.

Causes of Pediatric ESRD

The largest single disease group causing ESRD (Table VIII-3) in children is primary glomerulonephritis (31.7 percent of all reported causes), followed by cystic/hereditary/congenital diseases (24.4 percent). Hypertension only represented 5.0 percent of all pediatric ESRD. Diabetes is an extremely rare cause of ESRD in the pediatric population; only 1 in 2000 patients with ESRD due to diabetes falls in this age group. The distribution of causes of ESRD by age group for the pediatric patients incident during 1992-96 is shown in Figure VIII-3. Among the younger patients, 0-4 years old, cystic/hereditary/ congenital disease was the primary cause of ESRD. Among the older patients, 5-19 years of age at onset of ESRD, glomerulonephritis (GN) and collagen vascular diseases was prominent.

Figure VIII-3

Phase IV Commitment



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 20-955

Food and Drug Administration
Rockville MD 20857

R & D Laboratories. Incorporated
Attention: Rhoda Makoff. Ph.D.
4640 Admiralty Way. Suite 710
Marina del Ray, CA 90292

FEB - 5 1999

Dear Dr. Makoff:

Please refer to your new drug application dated December 23. 1997, received December 30, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferrlecit® (sodium ferric gluconate complex in sucrose injection) 62.5mg/5ml.

We request that you commit, in writing, to providing the following information post-approval:

1. Clarify whether or not the calibration curve for the method for Apparent Molecular Weight is a straight line (page 0631, Volume 14.2, Attachment V of the August 19, 1998 submission) or a curved line (page 169, Volume 1.4. of the December 23, 1997 submission). If it is a curved line, please discuss any additional mathematical treatment employed to calculate the molecular weight values.

2. When sufficient stability data are available for extension of the 12-month expiry, please provide these data in a prior approval supplemental application.

3. Clarify whether packaging component test procedure [redacted] Normal Inspection Level I. applies only to one in ten shipments. and that test procedure [redacted] Reduced Inspection Level I. will be used for all other shipments.

Please commit to providing this information within six months of the approval date for this application.

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

Sincerely yours.

/S/ [redacted]

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

NDA 20-955

R & D Laboratories, Incorporated
Attention: Rhoda Makoff, Ph.D.
4640 Admiralty Way, Suite 710
Marina del Rey, CA 90292

NOV - 2 1998

Dear Dr. Makoff:

Please refer to your new drug application dated December 23, 1997, received December 30, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferrlecit® (sodium ferric gluconate complex in sucrose injection) 62.5mg/5ml.

We acknowledge receipt of your submission dated June 9, 1998.

We request that you commit, in writing, to conducting the following studies or gathering the following information post-approval:

1. a Segment I. intravenous fertility and reproductive performance study in the rat;

2. a 13-week intravenous subchronic toxicity study in the dog;

3. a pilot human pharmacokinetic study of Ferrlecit®;

4. a study to determine the optimal dosing regimen for patients requiring repeated courses of Ferrlecit® for the achievement of iron repletion and for the maintenance of iron repletion;

5. a study to determine the safe and effective dosing regimen in the pediatric population;

6. a study to provide additional safety data such as the study described in the draft protocol entitled, "Cross over, Randomized, Blinded, Prospective, Multicenter, Clinical Evaluation of the Rate of Serious Allergic Reactions and Other Serious Adverse Effects to Ferrlecit Injection in iron deficient, anemic, hemodialysis patients as compared to placebo", included in the August 19, 1998 submission;

7. and gathering additional information (i.e., literature reports, adverse drug reaction reports) concerning the possibly increased risk of allergic/anaphylactic reactions in patients receiving ACE inhibitors and Ferrlecit® concurrently.

We recommend that draft protocols for the studies described above be submitted to the Agency for review and comment prior to initiation of the studies. Finalized study protocols, incorporating Agency comments and recommendations, should be submitted to IND [redacted]. Please include a proposed schedule for the initiation and completion of these studies as well as the submission of final study reports or requested information.

If you have any questions, please contact Brian Strongin, Regulatory Health Project Manager, at (301) 443-0483.

Sincerely yours,

/S/ [redacted]

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

[redacted]
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ATTACHMENT 1

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high-dose Ferrlecit, while significant increases from baseline in the low-dose group occurred only for hematocrit and serum ferritin (based on paired t-test analysis). When compared with the low-dose group, changes from baseline to endpoint in mean hemoglobin, hematocrit, percent iron saturation, MCH, and MCV were significantly better for the high-dose group. Further, analysis of mean changes over time for hemoglobin, hematocrit, and percent iron saturation were significantly higher for the high-dose group than those for the low-dose group. This analysis demonstrates that, throughout the study and at all time points, high-dose Ferrlecit was superior to low-dose in effectively treating anemia in iron deficient dialysis patients.

For both dose groups, when data were analyzed over the entire time course of the study, mean changes for hemoglobin and hematocrit indicated significant clinical improvement over time and none of the efficacy variables indicated worsening clinical status. A higher baseline rHuEPO dose contributed a significant effect on increases in hemoglobin and in hematocrit in the dose-control phase of the study, which is explored in the analyses of confounding factors and discussed in detail in the section on "rHuEPO-sparing" effect of iron administration.

Evidentiary Support for Maintenance Dosing After One Gram of Ferrlecit

As noted in the introduction, the National Kidney Foundation recently established a task force of independent physicians to review all available clinical data on the management of anemia in patients with chronic renal failure. The Dialysis Outcome Quality Initiative (DOQI) anemia guidelines were published in October, 1997 (34). These guidelines stress that many dialysis patients are unable to meet target hematocrits of 33-36% based on persistent iron deficiency notwithstanding improvement in laboratory parameters of iron deficiency following episodic intravenous iron supplementation. As pointed out by the guidelines, and summarized in the introduction, "no test exists" which adequately assesses iron status in the hemodialysis patient. This is because serum ferritin levels are uniformly elevated in patients with CRF beyond that traditionally associated with iron deficiency, and transferrin saturations respond acutely and variably to iron administration without providing an accurate assessment of available iron stores. Instead, DOQI guidelines recommend that 100 mg of iron be administered intravenously at every hemodialysis for 10 doses in patients who preliminarily meet entry criteria for iron deficiency anemia. These entry criteria (hematocrit < 33% on rHuEPO, ferritin < 100 ng/mL, and transferrin saturation (TSAT) < 20%) are nearly identical to those used in this study, although they permit a lesser degree of anemia and iron deficiency.

The DOQI guidelines state that, following administration of 0.5-1.0 gram of intravenous iron to such a patient, if the patient does not reach target hematocrit, the following course should be undertaken:

If in response to this course of iron there is no increase in Hct/Hgb and no increase in serum ferritin and TSAT level, at the same dose of Epoetin, a second course of IV iron should be tried. If, in response to this second course of IV iron, there is still no increase in Hct/Hgb, but either TSAT or serum ferritin level increases, then the weekly dose of IV iron should be reduced to the lowest amount required to maintain the TSAT ≥20% and the serum ferritin ≥ 100 ng/mL. If, on the other hand, in response to either of these courses of IV iron, there is an increase in Hct/Hgb at a constant dose of Epoetin, or a stable Hct at a decreased dose of Epoetin, then it is reasonable to administer 50 to 100 mg of iron IV once per week for 10 weeks again in an effort to achieve and maintain the Hct/Hgb at 33-36%/11-12 g/dL.

The dose control phase of this study provides further evidentiary support for these consensus guidelines. The mean hematocrit and hemoglobin values of patients in this study did not reach the DOQI target levels of 33-36%/11-12 g/dL at any time point. The patients in this study, despite statistically significant improvement, did not have resolution of anemia. Further, although there was significant improvement in TSAT in the high-dose group, and significant improvement in serum ferritin levels in both groups, in neither group did these laboratory parameters of iron deficiency reach levels at which the DOQI guidelines recommend cessation of further iron therapy. And, even with high-dose therapy, despite statistically significant improvement in hematocrit and hemoglobin at all days, iron saturation began to decline by Day 47 (from 16% at baseline to a peak level of 24-25% to a final level of 21%). In the low-dose group, TSAT at the end of the study was nearly identical to that at baseline (Figure 1). Similarly, in both patient groups, peak serum ferritin levels were achieved between days 19 and 31, and levels began to decline at Day 47 (Figure 2).

In this study, therefore, 30 days after completion of administration of 1 gram of iron, patients remained iron deficient and anemic by current standards notwithstanding significant improvement in iron deficiency and anemia as a result of therapy. Thus, these patients have demonstrated a need for greater than 1 gram of iron administration.

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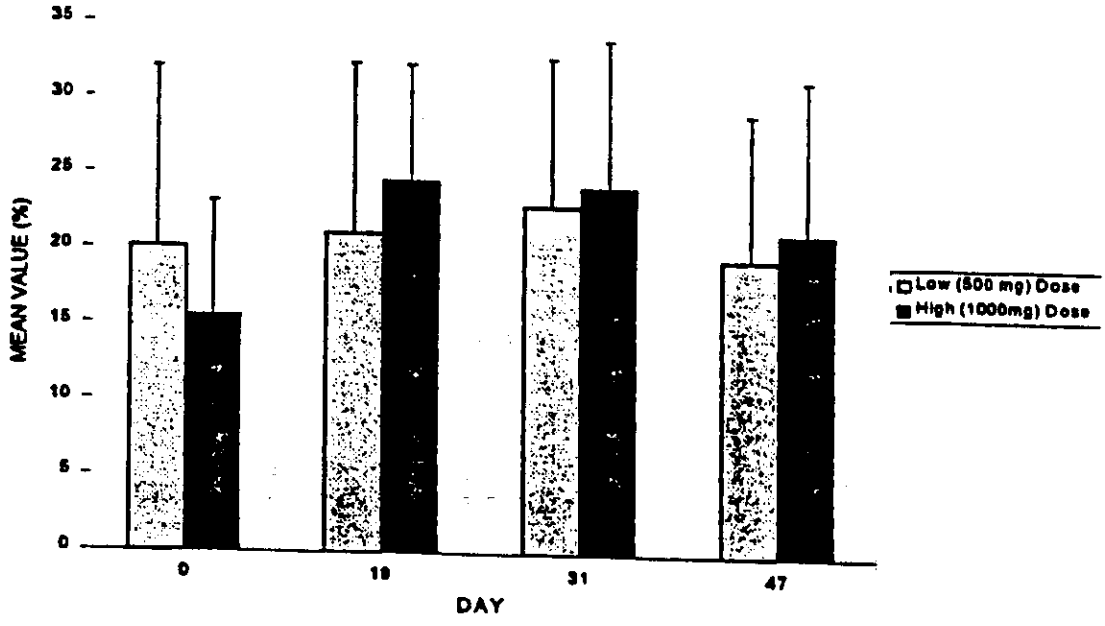

Figure 1. Mean values for percent iron saturation in patients receiving low- or high-dose Ferrlecit.

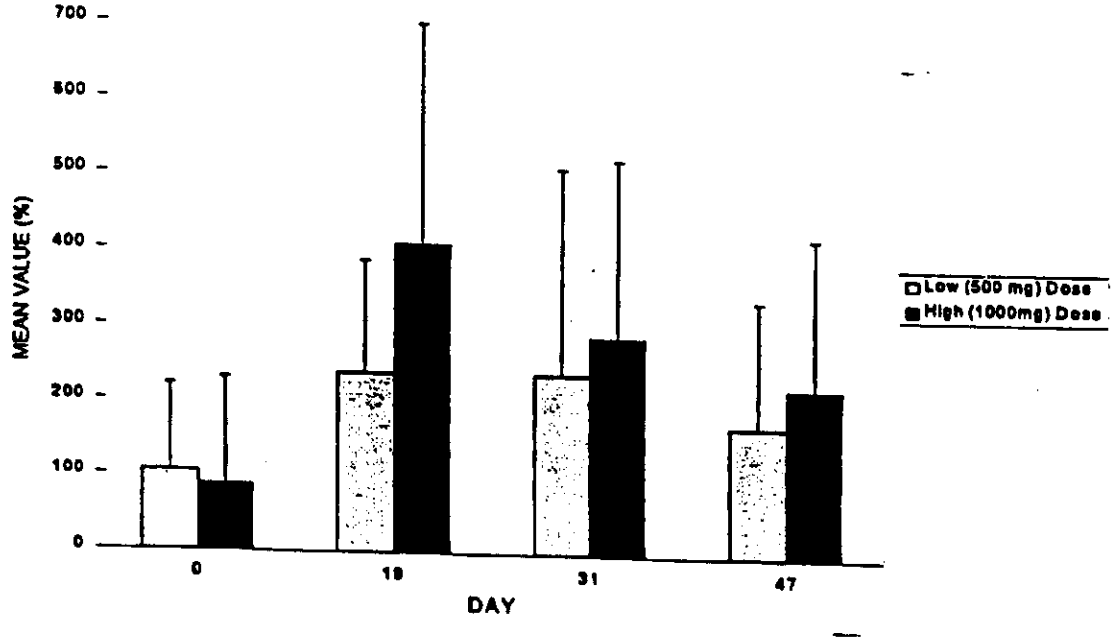

Figure 2. Mean values for serum ferritin in patients receiving low- or high-dose Ferrlecit.

Further support for this continuing deficiency can be found in the fact that hemodialysis patients randomized to treatment with only 500 mg of Ferrlecit demonstrate near-normalization of laboratory parameters at the earliest efficacy time points despite minimal or only temporary improvement in hematocrit. In short, these patients continued to be iron deficient. As shown by the demographically and otherwise comparable, randomized, high-dose control group, empiric administration of an additional 500 mg of Ferrlecit to the low-dose patients would have resulted in significant increases in hemoglobin and hematocrit. In the low-dose patients, this study, in effect, created a patient population with "functional" iron deficiency. A total dosage of 500 mg was inadequate to significantly correct anemia despite improvement in parameters of iron stores. The lower dosage group, therefore, unveiled and proved the existence of functional iron deficiency.

This study provides evidentiary support for continued intravenous iron administration to iron deficient anemic hemodialysis patients on rHuEPO until either of the following events are reached: (1) target hematocrits of 33-36% are achieved; or, (2) any laboratory indicators of even the smallest potential of acute or chronic iron overload are present. The latter occurs by medical consensus at transferrin saturation levels of > 50% or serum ferritin levels of > 800 ng/mL.

8.4.1.3 Historical (oral-dose) control Phase, Intent-to-treat Patients

1. Analysis of Covariance of Mean Change in Hemoglobin. Changes in hemoglobin from baseline to endpoint for the 3 treatment groups are summarized in Table 10. The mean change in hemoglobin from baseline to endpoint was significantly greater in the high-dose group than that in the low-dose group ($p=0.002$) or that in the historical (oral-dose) control group ($p=0.001$). No significant difference in mean change in hemoglobin was observed between the low-dose and historical control groups. Increases in hemoglobin from baseline to endpoint were significant for the high-dose group (high-dose $p<0.001$) and for the historical control group ($p=0.016$). No significant effect of age category was observed in subgroup analyses. Results from individual investigator sites are displayed in Table 10a. Significant differences between the high- and low-dose groups ($p<0.001$) and between the high-dose and historical control groups ($p=0.013$) occurred at the Lindsay site. At the Nissenson site, a significant difference occurred between the high-dose and historical control groups ($p=0.002$). No other significant differences between groups occurred, and the differences between the low-dose and historical control groups were not significant at any site.

2. Influence of Baseline rHuEPO Dose on Change in Hemoglobin. The possible influence of baseline rHuEPO dose was examined by using an ANCOVA. The baseline level significantly influenced change in hemoglobin

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(2)

8.4.1.5 Analyses of Confounding Factors (Dose-Control Phase)

Patients in the dose-control phase all received investigational drug substance as well as rHuEPO. Both drug substances are intended to treat anemia, and could be expected to cause independent effects on the primary efficacy measure of hemoglobin. Therefore, in the primary analysis, the influence of baseline rHuEPO on efficacy variables was analyzed using an ANCOVA. This analysis demonstrated that baseline rHuEPO significantly influenced change in hemoglobin as was expected (Section 8.4.1.1). At entry, patients were accepted as long as rHuEPO administration levels were less than or equal to 10,000 units three times per week. This resulted in entry of patients with varying baseline rHuEPO administration levels from 3,000 units to 10,000 units. Further, 22 patients required changes in rHuEPO notwithstanding that the protocol forbade rHuEPO changes.

During consultation with FDA, a request was made to analyze the relative effect of rHuEPO and intravenous iron administration from the data set obtained from this study in order to determine the level of rHuEPO-sparing effect that appropriate use of intravenous iron might have on anemic dialysis patients with signs of iron deficiency. The two factors unintentionally introduced into this trial--variable baseline rHuEPO administration level and changes in rHuEPO administration--permit a retrospective analysis of the relative effects of baseline rHuEPO administration levels and therapeutic attempts to increase hemoglobin by manipulating administered rHuEPO, as compared to the administration of Ferrlecit. Consequent to the request by the FDA, a statistical model was applied in which the change in efficacy value was assumed to be influenced by variations in baseline efficacy value, study center, baseline rHuEPO dose, and the change in rHuEPO dose. Positive and negative coefficients were assumed to apply to, respectively, increases or decreases in weekly rHuEPO dosing strategy. This analysis demonstrated that the investigator's spontaneous changes in level of weekly administration of rHuEPO during the study had no demonstrable effect on the primary efficacy variable--change in hemoglobin. One can reasonably conclude from this analysis that, once anemic dialysis patients with iron deficiency are on intravenous iron, physician-ordered adjustments to rHuEPO doses are ineffective in the management of anemia.

Since change in rHuEPO dose did not significantly influence efficacy outcome, this factor was dropped and the analysis was rerun without this term. Using this model, the dose effect for Ferrlecit administration was significant at each time point (Days 19, up to 40, and up to 60) for each efficacy variable and for both the intent-to-treat data set and the retrospective subset of patients with stable rHuEPO dose. Results are summarized in Table 14. These data are striking, in light of the known effectiveness of rHuEPO and the relatively high doses of rHuEPO that many patients in the study were on. Further, all results indicated a more favorable clinical response following high-dose Ferrlecit treatment as compared to low-dose treatment.

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Table 14. Analyses of Confounding Factors (Dose-Control Phase)
Changes in Hemoglobin and Hematocrit from Baseline through Days 40 and 60

Data Set	Efficacy Variable	End-Point	Least Square Estimates 500 mg n	500 mg LSMEAN	500 mg SE	1000 mg LSMEAN	1000 mg SE	p-values* Baseline Efficacy	Baseline rHuEPO	Center	TMT	rHuEPO Change+
Intent-to-treat Patients	HGB	Day 19	83	0.17	0.21	0.67	0.22	<0.001	0.749	0.019#	0.006	0.421
		Day 40	83	0.34	0.20	0.94	0.22	<0.001	0.451	0.096	0.004	0.135
		Day 60	83	0.57	0.22	1.12	0.23	<0.001	0.192	0.437	0.020	0.381
	HCT	Day 19	83	0.73	0.62	2.21	0.65	<0.001	0.565	0.001#	0.006	0.354
		Day 40	83	1.70	0.61	3.46	0.64	<0.001	0.386	0.027#	0.005	0.251
		Day 60	83	1.81	0.66	3.31	0.68	<0.001	0.095	0.290	0.036	0.353
Stable-rHuEPO Patients	HGB	Day 19	61	0.45	0.16	0.91	0.15	<0.001	0.437	0.506	0.035	NA§
		Day 40	61	0.51	0.19	1.21	0.17	<0.001	0.228	0.522	0.005	NA
		Day 60	61	0.50	0.20	1.19	0.19	<0.001	0.123	0.687	0.011	NA
	HCT	Day 19	61	1.50	0.47	2.91	0.43	<0.001	0.244	0.194	0.025	NA
		Day 40	61	2.06	0.55	3.90	0.51	<0.001	0.137	0.236	0.013	NA
		Day 60	61	1.51	0.61	3.42	0.56	<0.001	0.031	0.993	0.020	NA

* p-values were from an ANCOVA.
\+ This was categorized as: -1=decreased dose, 0=no change, and +1=increased dose.
\# The treatment mean varied significantly across center, however, there were no significant interactions between treatment and center, so the treatment difference remained the same.
§ NA = Not Applicable.

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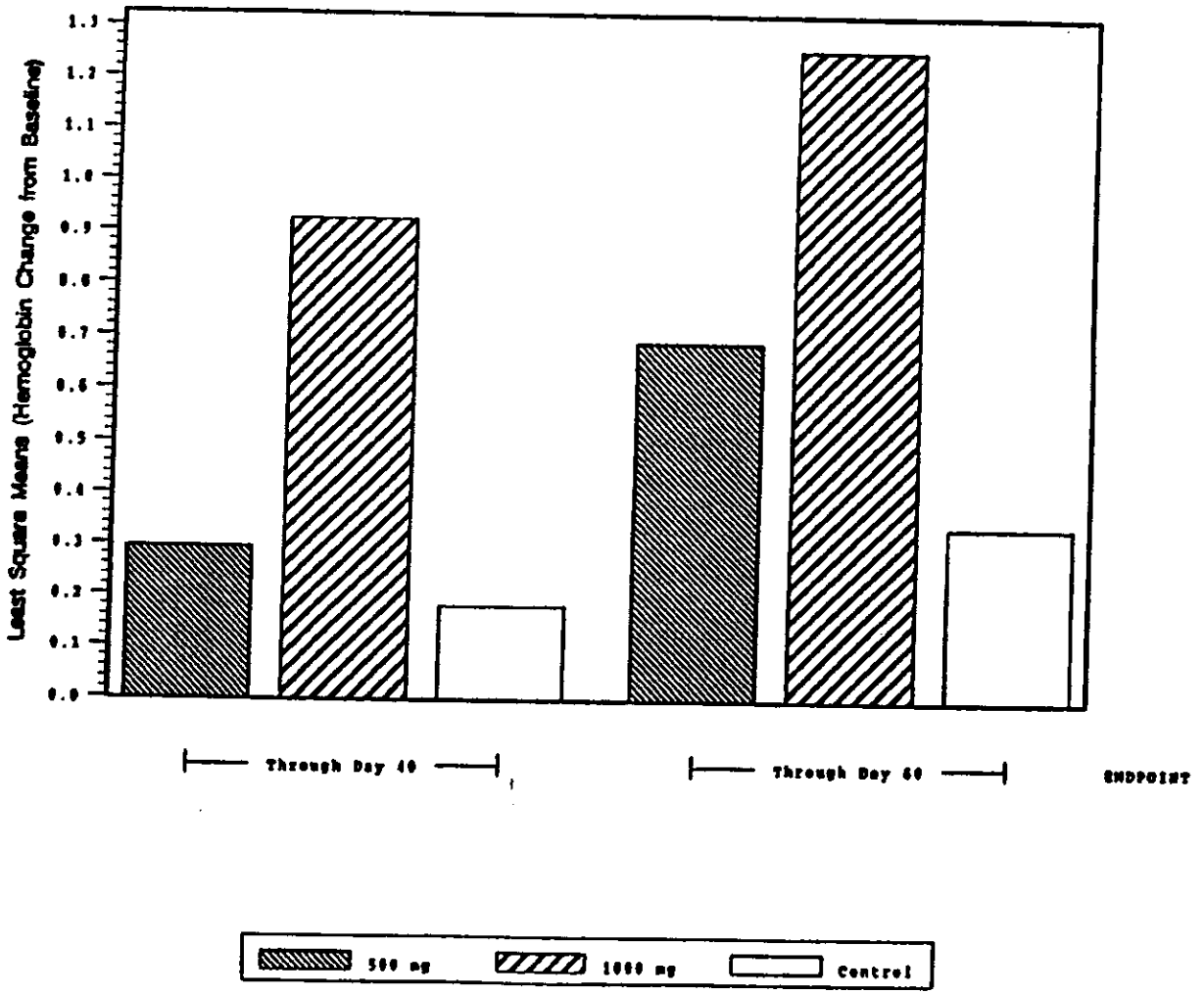
Table 15. Analyses of Confounding Factors (Historical (oral-dose) control Phase) Changes in Hemoglobin and Hematocrit from Baseline through Days 40 and 60

Data Set	Efficacy Variable	End-Point	Least Square Estimates: 500 mg n	500 mg LSMEAN	500 mg SE	1000 mg LSMEAN	1000 mg SE	Control LSMEAN	Control SE	p-values*: 500 vs. 1000	500 vs. Control	1000 vs. Control	Baseline Efficacy	Baseline rHuEPO	TMT	rHuEPO Change+
Intent-to-treat Patients	HGB	Day 40	107	0.29	0.19	0.92	0.20	0.18	0.27	0.002	0.662	0.003	<0.001	0.033	0.001	0.229
		Day 60	108	0.69	0.21	1.26	0.22	0.34	0.30	0.022	0.263	0.002	<0.001	0.145	0.004	0.407
	HCT	Day 40	107	1.29	0.57	3.15	0.60	0.49	0.79	0.003	0.301	<0.001	<0.001	0.011	<0.001	0.493
		Day 60	108	1.81	0.63	3.36	0.64	0.40	0.89	0.034	0.125	0.001	<0.001	0.021	0.002	0.433
Stable-rHuEPO Patients	HGB	Day 40	85	0.46	0.18	1.16	0.15	0.42	0.19	0.004	0.886	0.005	<0.001	0.035	0.003	NA#
		Day 60	86	0.57	0.21	1.29	0.18	0.33	0.23	0.012	0.460	0.002	<0.001	0.165	0.003	NA
	HCT	Day 40	85	1.74	0.52	3.53	0.45	0.94	0.56	0.011	0.308	0.001	<0.001	0.013	0.001	NA
		Day 60	86	1.46	0.63	3.38	0.54	0.38	0.66	0.022	0.249	0.001	<0.001	0.021	0.002	NA

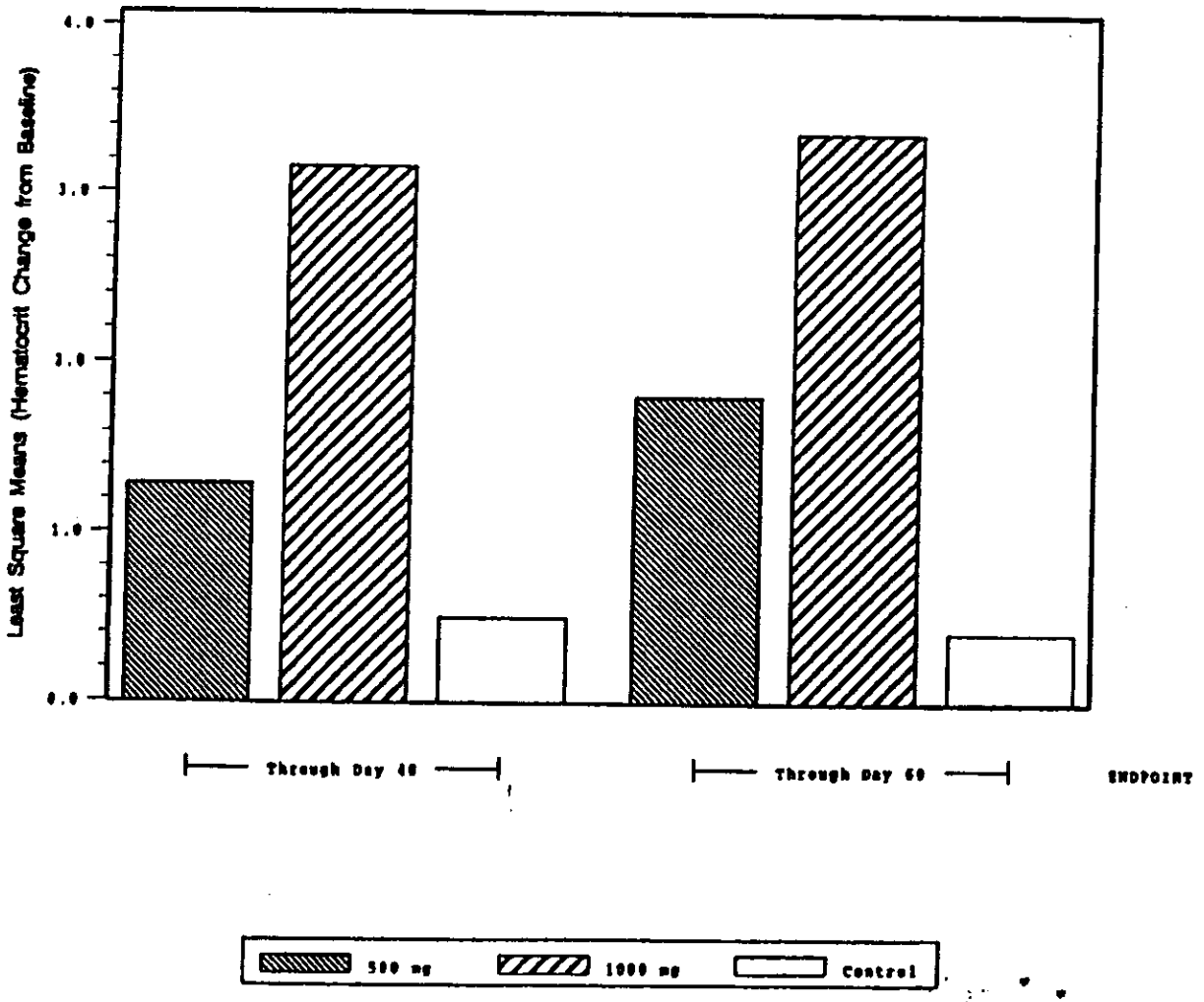
* p-values were from an ANCOVA.
\+ This was categorized as: -1=decreased dose, 0=no change, and +1=increased dose.
\# NA = Not Applicable.

Figure 5. Least Square Estimates of the Mean Hemoglobin Change from Baseline – Historical Control



Note: the least square estimates were from an analysis of covariance model with effects for baseline efficacy value, baseline EPO dose, dose group, and EPO change from baseline.

Figure 6. Least Square Estimates of the Mean Hematocrit Change from Baseline – a Historical Control



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Note: the least square estimates were from an analysis of covariance model with effects for baseline efficacy value, baseline EPO dose, dose group, and EPO change from baseline.

8.4.2 STATISTICAL/ANALYTICAL ISSUES

8.4.2.1 Adjustments for Covariates

For the historical (oral-dose) control phase, efficacy variables were analyzed by using ANCOVA, with the baseline efficacy variable as the covariate. For the dose-control and the historical (oral-dose) control phases, possible influence of baseline rHuEPO dose on change in efficacy variables was also analyzed by using ANCOVA, with baseline rHuEPO dose as the covariate.

8.4.2.2 Handling of Dropouts or Missing Data

For efficacy analyses, the last observation was carried forward when data were missing.

8.4.2.3 Multicenter Studies

This was a multicenter study involving 4 sites. The dose-control phase was performed at 3 sites (University of California at Los Angeles Medical School, Los Angeles, CA, Hennepin County Medical Center, Minneapolis, MN, and Victoria Hospital, London, Ontario, Canada), and the historical (oral-dose) control phase was performed at the University of Colorado Health Sciences Center, Denver, CO.

8.4.2.4 Multiple Comparison/Multiplicity

Only 1 primary efficacy variable was analyzed per study phase, by using 1 primary analysis. No adjustments for multiplicity of testing were necessary.

8.4.2.5 Use of an "Efficacy Subset" of Patients

In the dose-control phase of the study, efficacy analyses were performed on the intent-to-treat data set, obtained from 83 patients with baseline values and at least 1 value after baseline (Table 2). The data set did not include Patients 4, 116, 120, 311, and 335, who discontinued during the study, because only baseline variable data were available for these patients.

In the historical (oral-dose) control phase of the study, efficacy analyses were performed on data from the 83 patients in the dose-control phase plus the 25 patients in the historical (oral-dose) control group, for a total of 108 patients.

In both phases of the study, efficacy analyses were also performed on the per-protocol data set, which did not include 5 patients who discontinued the study,

3 patients who did not meet inclusion criteria, and 22 patients whose rHuEPO dose changed during the study (including 1 patient who did not meet inclusion criteria).

Analyses of confounding factors were performed on the intent-to-treat data set and on data obtained from patients whose rHuEPO dose did not change during the study. An analysis of change in hemoglobin was performed on data from patients who met the definition of "responder" (see Section 6.8).

8.4.2.6 Examination of Subgroups

Results of mean changes in hemoglobin for the intent-to-treat patients in the dose-control and historical (oral-dose) control phases of the study were analyzed by using ANOVA models that included the subgroups of race (white or other), gender, and age category (<51 years, 51-65 years, and >65 years for women, ≤65 years or >65 years for men).

8.4.3 TABULATION OF INDIVIDUAL RESPONSE DATA

The listing of primary and secondary efficacy variable results by individual patient is in Appendix 13.2.2.

8.4.4 EFFICACY CONCLUSIONS

Treatment with high-dose (1000 mg) Ferrlecit significantly improved hemoglobin and other hematologic indicators of anemia in ESRD patients on chronic hemodialysis when compared with low-dose Ferrlecit treatment and when compared with oral iron treatment. Treatment with low-dose (500 mg) Ferrlecit enhanced some blood parameters of study patients, but to a lesser degree than high-dose treatment.

In the analysis of intent-to-treat and per-protocol patients, mean changes in hemoglobin and hematocrit were similar between the data sets for both dose groups, indicating that the inclusion of protocol violators in the intent-to-treat group did not significantly affect study results. Similarly, comparison of the intent-to-treat group with the stable-rHuEPO group indicated that change in rHuEPO dose did not significantly impact results of Ferrlecit-treatment comparisons.

Further, the iron-deficient anemic patients in this study failed to reach clinically-appropriate target hematocrits, notwithstanding treatment with 1.0 gram of Ferrlecit, and continued to demonstrate signs of residual iron deficiency up to Day 60. In short, this study, as supported by other clinical data in the medical literature, demonstrates that patients meeting entry criteria remain iron deficient following the administration of 1 gram of Ferrlecit, notwithstanding significant improvement in iron deficiency and anemia as a result of therapy. Thus, this study demonstrated that

empiric therapy with Ferrlecit should continue after administration of 1 gram until either target hematocrits of 33-36% are achieved or any laboratory indicators of even the smallest potential of acute or chronic iron overload are present. The latter occurs at transferrin saturation levels of >50% or serum ferritin levels of >800 ng/mL.

The use of an historical (oral-dose) control, in which oral iron failed to be sufficiently effective, demonstrates that intravenous sodium ferric gluconate administered at a dosage of 1.0 gram over 8 consecutive dialysis sessions represents the first line of therapy for the anemic dialysis patient who develops signs of iron deficiency as shown by a transferrin saturation below 18% or a transferrin level below 100 ng/mL.

Appropriate therapy with Ferrlecit in the anemic dialysis patient with iron deficiency should preclude the need to use increases in rHuEPO dosage to achieve increases in hematocrit. The statistical model developed upon the instigation of FDA clearly demonstrates that EPO-sparing occurred in the patients in this study. Stated another way, a physician could have achieved equivalent final hemoglobin levels by either of two pathways in the patients entered into this study: (1) administer 500 mg of Ferrlecit and increase the rHuEPO dose by 5,000 units; or, (2) administer a full course of 1,000 mg of Ferrlecit. In sum, both drug substances--rHuEPO and Ferrlecit--were shown by this study to have independent and non-covarying impacts on improvement in hemoglobin in this patient population of chronic renal dialysis patients with blood parameters of iron deficiency anemia, although the effect of rHuEPO was small. These data are consistent with the magnitude of the EPO-sparing effect identified in earlier publications (43, 59, 60). Appropriate administration of Ferrlecit has been shown by this study to eliminate the need to increase rHuEPO administration to achieve increases in hematocrits or hemoglobins.

9. SAFETY EVALUATION

9.1 EXTENT OF EXPOSURE

Eighty-eight patients enrolled in the dose-control phase and received a test dose of 25 mg Ferrlecit prior to the beginning of the study. Forty-four patients received 1000 mg Ferrlecit, in 8 doses of 125 mg each. Thirty-nine patients received 500 mg Ferrlecit, in 8 doses of 62.5 mg each. Three patients discontinued the study prematurely; one received 375 mg (6 doses of 62.5 mg each), 1 received a single dose of 125 mg, and 1 received a single dose of 62.5 mg. Two patients received only the test dose before discontinuing.

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10. DISCUSSION AND OVERALL CONCLUSIONS

Ferrlecit was effective in improving hematologic indicators of anemia in chronic hemodialysis patients. Treatment with high-dose Ferrlecit resulted in a significant mean increase in hemoglobin from 9.6 g/dL at baseline to 10.7 g/dL at endpoint, which is considered a clinical improvement, although optimal levels of hemoglobin would be 12.0 g/dL. Mean increases for hematocrit, percent iron saturation, serum ferritin, serum iron, MCH, and MCV were also significant following treatment with high-dose Ferrlecit.

Treatment with low-dose Ferrlecit also resulted in a mean increase in hemoglobin from 9.8 g/dL at baseline to 10.1 g/dL at endpoint, although this change was not statistically significant. Mean increases for hematocrit and serum ferritin were significant with low-dose Ferrlecit treatment.

High-dose Ferrlecit was superior to low-dose Ferrlecit in improving patients' hematologic indicators of anemia. Baseline values for hemoglobin and for the secondary efficacy variables were similar between the 2 groups, except for percent iron saturation, which was significantly lower in the high-dose group. Mean changes from baseline to endpoint and mean changes over time for hemoglobin and for the majority of the secondary efficacy variables were significantly greater for the high-dose group than for the low-dose group. None of the changes in efficacy variables were higher for the low-dose group than for the high-dose group.

In the historical (oral-dose) control phase of the study, significant differences in changes in mean hemoglobin and mean hematocrit occurred between the high-dose group and both the low-dose and historical (oral-dose) control groups, but the differences between the low-dose group and the historical-control group were not significant. Two of 3 study sites independently showed significant improvement in hemoglobin as compared to the historical (oral-dose) control. The use of an oral-dose control, in which oral iron therapy failed to be sufficiently effective, demonstrates that intravenous sodium ferric gluconate administered at a dosage of 1.0 gram over 8 consecutive dialysis sessions represents the first line of therapy for the anemic dialysis patient who develops signs of iron deficiency as shown by a transferrin saturation below 18% or a serum ferritin level below 100 ng/mL.

In comparisons of the intent-to-treat and stable-EPO data sets, mean changes in hemoglobin and in hematocrit were similar, indicating that physician-initiated adjustments in rHuEPO dose during the study did not appreciably influence the efficacy outcome and that improvements in hemoglobin and hematocrit were due primarily to Ferrlecit treatment. In further analyses, both drug substances--rHuEPO and Ferrlecit--were shown to have independent and non-covarying impacts on improvement in hemoglobin in this patient population, although the effect of

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Taylor JE, et. al., "Regular low-dose intravenous iron therapy improves response to erythropoietin in hemodialysis patients," (Nephrol Dial Transplant 1996 11 1079)

In this 6-month study, 46 stable hemodialysis patients were treated with 62.5 mg of sodium ferric gluconate post-dialysis; twice-weekly, weekly, or every two weeks, depending on their serum ferritin levels. The effects on hemoglobin, serum ferritin, EPO dose, and iron dose were determined.

Of the 46 hemodialysis patients who participated in this study, 67% were male, and the median age was 67 years. All patients had received EPO for at least 6 months, with a stable EPO dose for at least 3 months. Patients were excluded for infection, malignancy, liver disease, or chronic inflammation. All patients had ferritin levels of < 600 µg/L, had not received a blood transfusion in the preceding 6 months, were taking oral iron, and had not received intravenous iron in the previous 3 months.

Patients were administered 62.5 mg of intravenous ferric gluconate twice weekly (for a ferritin of < 100 µg/L), weekly (for a ferritin of 100-250 µg/L), or every two weeks (for a ferritin of 250-600 µg/L). Study medication was given as a slow injection through the fistula needle at the end of dialysis. Oral iron supplements were discontinued. EPO doses were adjusted up or down by 30-50%, in order to maintain hemoglobin levels of 11-13 g/dL for male patients, and 10-12 g/dL for female patients.

Changes in hemoglobin, ferritin, EPO dose, and Ferric Gluconate dose over a 6-month period, in 34 patients with an initial ferritin of > 100 µg/L, are summarized below:

Changes in hemoglobin, ferritin, EPO dose, and Ferric Gluconate Dose for Patients with an Initial Ferritin of > 100 µg/L

	Pre haemoglobin (g/dl)	Post haemoglobin (g/dl)	Pre ferritin (µg/l)	Post ferritin (µg/l)	Pre erythropoietin (x 1000 i.u./wk)	Post erythropoietin (x 1000 i.u./wk)	Pre iron (ml/wk)	Post iron (ml/wk)
Median	9.85	11.25	176	304.5	6	4	5	2.5
Range	6.5–12.8	9.9–13.3	103–519	121–792	3–15	0–15	2.5–10	0–5
P		<0.0001		<0.0001		0.005		<0.0001

The mean hemoglobin increased from 9.8 g/dL to 11.3 g/dL. Mean EPO requirements decreased from 6000 U/week to 4000 U/week (Note that EPO doses were adjusted to maintain hemoglobin values in a prespecified range.) Mean Ferric Gluconate requirements decreased from 62.5 mg/week, to 31.25 mg /week.

Changes in hemoglobin, ferritin, EPO dose, and Ferric Gluconate dose over a 6-month period, in 12 patients with an initial ferritin of < 100 µg/L, are summarized below:

Changes in hemoglobin, ferritin, EPO dose, and Ferric Gluconate Dose for Patients with an Initial Ferritin of < 100 µg/L

	Pre haemoglobin (g/dl)	Post haemoglobin (g/dl)	Pre ferritin (µg/l)	Post ferritin (µg/l)	Pre erythropoietin (× 1000 i.u./wk)	Post erythropoietin (× 1000 i.u./wk)	Pre iron (ml/wk)	Post iron (ml/wk)
Median	10.05	11.00	68	210.5	9	6	10	2.5
Range	8.5–11.9	9.9–11.9	20–96	91–447	4–30	2–10	5–10	1.25–10
P	0.05		0.001		0.05		0.005	

The mean hemoglobin increased from 10.1 g/dL to 11.0 g/dL. Mean EPO requirements decreased from 9000 U/week to 6000 U/week (Note that EPO doses were adjusted to maintain hemoglobin values in a prespecified range.) Mean Ferric Gluconate requirements decreased from 125 mg/week, to 31.25 mg/week.

No adverse events were reported in this study.

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Nephrol Dial Transplant 1995 Nov;**10(11)**:2070-2076

Importance of iron supply for erythropoietin therapy.

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Department of Medicine, University of Vienna, Austria.

BACKGROUND. rHuEpo and iron therapy corrects renal anaemia. However, dosage, route of administration, and monitoring of iron and rHuEpo therapy in uraemic patients remains controversial. METHODS. Therefore a 22-month i.v. iron substitution trial, subdivided into four study periods, was initiated in 64 iron-depleted chronic haemodialysis (HD) patients receiving i.v. rHuEpo therapy. Within the first period (6 months) patients were treated with high-dose iron (100 mg at the end of HD treatment, mean cumulative i.v. iron saccharate dosage was 2538 +/- 810 mg per patient) in order to replete the iron stores. During the 2nd period (6 months) the available iron pool was maintained with low-dose iron by administration of 10, 20, or 40 mg iron at each HD, depending on haemoglobin, serum ferritin and transferrin saturation levels. During the 3rd period (4 months), the iron-replete patients were randomized to i.v. or s.c. route of rHuEpo administration. During the 4th period (3 months) iron substitution was omitted to exclude severe iron overload. RESULTS. In the first study period, high-dose iron therapy dramatically reduced the weekly rHuEpo requirement by 70% of the initial dose (from 217 +/- 179 to 62.6 +/- 70.2 U/kg/week). In the 2nd period iron storage pools were easily maintained. Serum ferritin and transferrin saturation levels remained stable during this study period. Randomization for thrice-weekly i.v. or s.c. administration of rHuEpo in the 3rd study period revealed comparable efficacy for both administration routes in iron-replete patients. In well-nourished patients (serum albumin > 40 g/l) without hyperparathyroidism (parathyroid hormone levels < 100 pg/ml), 50-60 U/kg/week rHuEpo were required in contrast to > 100 U/kg/week in patients with hyperparathyroidism. In the 4th study period, withdrawal of iron administration led to a rapid decrease of serum ferritin and transferrin saturation levels, indicating the absence of severe iron overload. CONCLUSIONS. Long-term thrice-weekly i.v. low-dose iron therapy (10-20 mg per HD treatment) proved to be a very effective, economical and safe treatment schedule for iron-replete HD patients. Intravenous and s.c. rHuEpo therapy was equally efficacious in iron-replete, well-nourished patients. HD patients with increased parathyroid hormone levels require significantly more rHuEpo than HD patients with parathyroid hormone levels values < 100 pg/ml).

Publication Types:

- Clinical trial
- Randomized controlled trial

PMID: 8643170, UI: 96227346

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Nephrol Dial Transplant 1996 Feb;11(2):319-322

Economic appraisal of maintenance parenteral iron administration in treatment of anaemia in chronic haemodialysis patients.

Sepandj F, Jindal K, West M, Hirsch D

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BACKGROUND. Iron deficiency is common in haemodialysis patients and adequate supplementation by the oral or parenteral route has been limited by drug side-effects, absorption, and cost. Intermittent doses of intravenous iron dextran complex are recommended in patients with inadequate iron stores despite maximal tolerated oral dose. We conducted a prospective study with economic analysis of a regular maintenance intravenous iron regimen in this group of patients. METHODS. Fifty patients comprising one-half of our haemodialysis population required intravenous iron treatment, i.e. they failed to achieve an arbitrary goal serum ferritin 100 microg/l despite maximal tolerated oral iron dose. After a loading dose of intravenous iron dextran complex (IV-FeD) based on Van Wyck's nomogram (400+/-300 mg) they received a maintenance dose of 100mg IV-FeD once every 2 weeks. Initial goal serum ferritin was set at 100-200 microg/l. If no increase in haemoglobin was achieved at this level, transferrin saturation was measured to assess bioavailable iron, and when less than 20%, goal serum ferritin was increased to 200-300 microg/l. Recombinant human erythropoietin (rHuEpo) was used where needed to maintain haemoglobin in the 9.5-10.5 g/l range only if ferritin requirements were met. Results. Mean haemoglobin rose from 87.7+/-12.1 to 100.3+/-13.1 g/l (P<0.001, CI 7.7-17.9) at mean follow-up of 6 months (range 3-15 months). In patients on rHuEpo, dose per patient was reduced from 96+/-59 u/kg per week to 63+/-41 u/kg per week, representing a 35% dose reduction (P<0.05, CI 1-65). An annual cost reduction of $3166 CDN was projected; however, in the first year this is offset by the cost of the loading dose of IV-FeD required at the beginning of treatment. No adverse reactions were encountered. CONCLUSION. Iron deficiency is very common in our haemodialysis population, especially in those patients receiving rHuEpo. A carefully monitored regimen of maintenance parenteral iron is a safe, effective, and economically favourable means of iron supplementation in patients with insufficient iron stores on maximum tolerated oral supplements.

PMID: 8671786, UI: 96325190

ATTACHMENT 8

SUMMARY AND CONCLUSIONS

Two sponsor-conducted studies were submitted to support the approval of Ferrlecit as **"first line treatment for iron deficiency anemia in renal hemodialysis patients on supplemental recombinant human erythropoietin"**: studies 5600-01 and 5600-03.

Study 5600-01 was a 3-center, randomized, open-label, historically-controlled, comparative study of a high- and low-dose i.v. Ferrlecit regimen, in 108 iron-deficient chronic hemodialysis patients. Study 5600-03 was a single-center, non-randomized, open-label, variable-dose, compassionate-use, historically-controlled study of the use of i.v. Ferrlecit in 63 iron-deficient chronic hemodialysis patients. Additional studies, including 252 Ferrlecit-treated patients from the published literature, and postmarketing information from Europe, were also submitted to support the safety and efficacy of Ferrlecit in chronic renal dialysis patients.

Summary of Study 5600-01

Study 5600-01 was a 3-center, randomized, open-label, historically-controlled, study of the safety and efficacy of 500 mg (low-dose) and 1000 mg (high-dose) of Ferrlecit® in iron-deficient hemodialysis patients. Study medication was given in 8 divided doses, during 8 sequential dialysis sessions (or a period of 16 to 17 days). The primary endpoint was the change in hemoglobin from baseline to the last available observation through Day 40.

Eligibility for this study (including protocol amendments) included chronic hemodialysis patients with a hemoglobin below 10 g/dL (or hematocrit at or below 32%), and serum ferritin below 100 ng/mL or iron saturation below 18%. Exclusion criteria included significant underlying disease or inflammatory conditions, or an EPO requirement of greater than 10,000 units t.i.w. Parenteral iron and red cell transfusions were not allowed for 2 months prior to, and during the study. Oral iron was not allowed for Ferrlecit-treated patients.

The historical control population consisted of 25 chronic hemodialysis patients associated with the University of Colorado Health Sciences Center. Due to drug unavailability, intravenous iron dextran was discontinued in these patients for 14 months. All patients were to have stable EPO doses and hematocrit values for at least 2 months prior to iron dextran discontinuation, however "many of the patients received blood transfusions before the beginning of the study". All patients received oral iron supplementation throughout the study, although dose and patient

compliance were not monitored. Safety data was not collected.

The intent-to-treat population consisted of 39 patients in the low-dose Ferrlecit group, 44 patients in the high-dose Ferrlecit group, and 25 historical control patients. Three patients in the low-dose group were enrolled but did not meet the inclusion criteria (hemoglobin or ferritin levels were too high).

A total of 5 patients were withdrawn from the study. Two discontinued for logistic reasons. One patient was withdrawn after development of pruritis and chest pain following the test dose. One patient in the high-dose group was withdrawn following the development of nausea, abdominal pain, flank pain, fatigue, and rash following the first treatment dose. One patient in the low-dose group was withdrawn after the development of a "red, blotchy rash" following the first treatment.

Ten EPO dosage changes occurred during the course of study drug administration: 4 patients had increases, and 2 patients had decreases in their EPO doses in the low-dose group; and 3 patients had increases, and 1 patient had a decrease in their EPO doses in the high-dose group.

Fourteen EPO dosage changes occurred after the administration of study drug: 6 patients had increases, and 2 patients had decreases in their EPO doses in the low-dose group; and 2 patients had increases, and 4 patients had decreases in their EPO doses in the high-dose group.

Thus, the per-protocol population consisted of 24 low-dose Ferrlecit patients, 35 high-dose Ferrlecit patients, and 25 historical control patients. These numbers represent 59%, 78%, and 100%, of the intent-to-treat low-dose, high-dose, and historical control populations, respectively.

Patient populations were similar with respect to baseline demographics, hemoglobin, hematocrit, iron studies, and red blood cell indices, with the exception that there were more white Ferrlecit-treated patients, and the serum ferritin was significantly higher in historical control patients (605.6 ng/mL in historical control patients, compared to 105.6 ng/mL in low-dose and 88.4 ng/mL in high-dose patients).

The mean baseline hemoglobin and hematocrit were similar between treatment and historical control patients, and were 9.6 g/dL, and 29%, respectively.

Mean changes in hemoglobin from baseline were small (0.3 g/dL in the low-dose, and 1.1 g/dL in the high-dose intent-to-treat patients; and 0.5 g/dL in the low-dose, and 1.2 g/dL in the

high-dose per-protocol patients).

Mean changes in hemoglobin from baseline, for both the intent-to-treat and per-protocol populations, increased within each dose group, and were greater in the high-dose compared to the low-dose Ferrlecit groups.

When compared to the historical control, mean changes in hemoglobin from baseline, for both the intent-to-treat and per-protocol populations, were higher for the high-dose compared to either low-dose or historical control patients. Mean changes in hemoglobin from baseline were similar in the low-dose and historical control patients.

The observed increases in hemoglobin were supported by the results for the hematocrit and iron studies, for both the intent-to-treat and per-protocol patients. Specifically, serum iron, percent iron saturation, and serum ferritin increased by 11.7 µg/dL, 8.5%, and 199.4 ng/mL, respectively, in high-dose intent-to-treat patients; and 10.8 µg/dL, 8.3%, and 175.1 ng/mL, respectively, in high-dose per-protocol patients.

No treatment-by-investigator interactions were reported, and no significant associations of age, race, or gender were found for the observed increases in hemoglobin from baseline.

ANCOVA analyses designed to determine the effects of confounding variables on the primary efficacy outcome, found that the baseline hemoglobin, and dose of Ferrlecit (high-dose > low-dose); and NOT changes in EPO dose, had significant effects on the observed increases in hemoglobin. Because a significant effect of baseline EPO dose on the change in hemoglobin was noted in the analysis which included results from historical control patients, an ANCOVA analysis which included the covariates of treatment effect, baseline hemoglobin, baseline EPO dose, and change in EPO dose, was performed. This analysis reconfirmed the significantly greater increases of hemoglobin and hematocrit in high-dose, compared to low-dose or historical control patients.

The primary Ferrlecit-associated adverse events were allergic reactions that occurred in 3 patients, and resulted in premature study discontinuation. Available information for these cases is shown below:

Patient	Reasons for Study Discontinuation
116	Patient withdrew after the development of pruritis and chest pain following the test dose of Ferrlecit.
311	Patient was in the high-dose group, and experienced nausea, abdominal and flank pain, fatigue, and rash following the first dose of Ferrlecit.
335	Patient was in the low-dose group, and experienced a "red, blotchy rash" following the first dose of Ferrlecit.

The incidence of patients who experienced an allergic reaction in this study was 3/83 Ferrlecit-treated patients, or 3.6%. No anaphylactoid reactions, i.e. those including hypotension, edema, dyspnea, or cardiac arrest, were reported.

Summary of Study 5600-03

Study 5600-03 was a single-center, non-randomized, open-label, historically-controlled, variable-dose, compassionate-use study of the safety and efficacy of Ferrlecit in iron-deficient hemodialysis patients. 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 5600-01, as was the historical control population. Sixty-three patients were evaluated in this study: 38 in the Ferrlecit-treated group, and 25 patients in the historical control group.

Ferrlecit-treated patients were considered to have completed the study per protocol, if they received at least 8 doses of study medication. A total of 14(37%) of completed the study per protocol. Twelve (32%) Ferrlecit-treated patients received less than 8 doses, and 12(32%) patients had incomplete dosing information. Not all patients received Ferrlecit at consecutive dialysis sessions, and many Ferrlecit-treated patients received oral iron during the study (no further information was provided).

Overall the Ferrlecit-treated group was comprised of more: males, males of age ≤ 65 years, and Caucasians. The mean weight of Ferrlecit-treated patients was 180 kg, compared to a mean weight of 144 kg in historical control patients.

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.

Mean increases in hemoglobin from baseline were small, and similar to those seen observed in study 5600-01; 0.4 g/dL in historical control patients, and 1.3 g/dL in Ferrlecit-treated patients. Within-in group changes in hemoglobin were statistically significant for Ferrlecit-treated, and not historical control patients.

Non-statistically-significant increases in serum iron, percent iron saturation, and serum transferrin were noted in Ferrlecit-treated patients.

No significant effect of age or race on changes in hemoglobin or hematocrit were reported. A significant treatment-by-gender interaction was noted for female patients however: females in the Ferrlicit-treated group had significantly greater increases in hemoglobin and hematocrit, than females in the historical control group). Changes in hemoglobin were not significantly affected by baseline EPO doses.

Of the 38 patients exposed to Ferrlecit in this study, 1 patient experienced an adverse event(s) that resulted in premature study discontinuation, required hospitalization, and was felt by the on-site investigator to be "probably" related to study drug. Specifically, patient #552 discontinued due to "dizziness, lightheadedness, diplopia, malaise, and weakness", after receiving a total of 125 mg of Ferrlecit.

In summary, interpretation of the results of Study 5600-03 is limited by the fact that this study was a small, single-center, compassionate-use, variable-dose, historically-controlled trial. However, the results of study 5600-03 corroborate the results of study 5600-01, and thus support the efficacy of Ferrlecit for iron replacement therapy in chronic hemodialysis patients.

ATTACHMENT 9

(9)

OTHER STUDIES TO SUPPORT THE EFFICACY OF FERRLECIT

Published Reports

Five published reports were submitted to support the efficacy of Ferrlecit in treating iron deficiency in chronic hemodialysis patients. These studies are discussed below.

Navarro JF, et. al., "Effectiveness of Intravenous Administration of Fe-Gluconate-Na Complex to Maintain Adequate Body Iron Stores in Hemodialysis Patients," Am J Neph 1996 16 268

This 6-month study prospectively examined the effects of the monthly administration of 62.5 mg of sodium ferric gluconate, on body iron stores in chronic hemodialysis patients.

Fifty-eight patients were enrolled; 31 of these patients were excluded for the following reasons: chronic hepatitis (n=8), chronic inflammatory diseases (n=2), intercurrent infection during the follow-up period (n=4), external blood losses (n=5), red blood cell transfusion requirement (n=6), and variations of the monthly hemoglobin of ≥ 1 g/dL (n=6).

Of the 27 remaining evaluable patients; half were female, the mean age was 57 years, and all were on hemodialysis for more than 2 years. Sixteen (60%) patients were on a stable EPO maintenance doses.

Study drug was administered monthly, as 62.5 mg in 50 ml of saline, given over 30 minutes at the end of dialysis.

The results are shown below (vol. 25, p. 194). Note that "iron stores" in the table below was calculated from the modified formula of Cook et. al. (Nephrol Dial Transplant 1993 8 846): iron stores (in mg) = 400 x ln (serum ferritin in mg/L ÷ 50)

Parameter	Basal	Time, months		
		2	4	6
Hemoglobin, g/dl	10.7±1.1	10.7±1.2	10.7±1.2	10.6±1
Hematocrit, %	32.8±3.8	32.8±4.5	32.5±3.9	32.3±3
Ferritin, µg/l	187±96	203±96	230±120	196±115
Iron stores, mg	457±273	461±205	470±199	451±316

p = NS for all parameters.

No significant differences in hemoglobin, hematocrit, ferritin, or (calculated) iron stores, were observed. No allergic or other adverse events were reported.

Taylor JE, et. al., "Regular low-dose intravenous iron therapy improves response to erythropoietin in hemodialysis patients," (Nephrol Dial Transplant 1996 11 1079)

In this 6-month study, 46 stable hemodialysis patients were treated with 62.5 mg of sodium ferric gluconate post-dialysis; twice-weekly, weekly, or every two weeks, depending on their serum ferritin levels. The effects on hemoglobin, serum ferritin, EPO dose, and iron dose were determined.

Of the 46 hemodialysis patients who participated in this study, 67% were male, and the median age was 67 years. All patients had received EPO for at least 6 months, with a stable EPO dose for at least 3 months. Patients were excluded for infection, malignancy, liver disease, or chronic inflammation. All patients had ferritin levels of < 600 µg/L, had not received a blood transfusion in the preceding 6 months, were taking oral iron, and had not received intravenous iron in the previous 3 months.

Patients were administered 62.5 mg of intravenous ferric gluconate twice weekly (for a ferritin of < 100 µg/L), weekly (for a ferritin of 100-250 µg/L), or every two weeks (for a ferritin of 250-600 µg/L). Study medication was given as a slow injection through the fistula needle at the end of dialysis. Oral iron supplements were discontinued. EPO doses were adjusted up or down by 30-50%, in order to maintain hemoglobin levels of 11-13 g/dL for male patients, and 10-12 g/dL for female patients.

Changes in hemoglobin, ferritin, EPO dose, and Ferric Gluconate dose over a 6-month period, in 34 patients with an initial ferritin of > 100 µg/L, are summarized below:

Changes in hemoglobin, ferritin, EPO dose, and Ferric Gluconate Dose for Patients with an Initial Ferritin of > 100 µg/L

	Pre haemoglobin (g/dl)	Post haemoglobin (g/dl)	Pre ferritin (µg/l)	Post ferritin (µg/l)	Pre erythropoietin (x 1000 I.u./wk)	Post erythropoietin (x 1000 I.u./wk)	Pre iron (ml/wk)	Post iron (ml/wk)
Median	9.85	11.25	176	304.5	6	4	5	2.5
Range	6.5–12.8	9.9–13.3	103–519	121–792	2–15	0–15	2.5–10	0–5
P		<0.0001		<0.0001		0.005		<0.0001

The mean hemoglobin increased from 9.8 g/dL to 11.3 g/dL. Mean EPO requirements decreased from 6000 U/week to 4000 U/week (Note that EPO doses were adjusted to maintain hemoglobin values in a prespecified range.) Mean Ferric Gluconate requirements decreased from 62.5 mg/week, to 31.25 mg /week.

Changes in hemoglobin, ferritin, EPO dose, and Ferric Gluconate dose over a 6-month period, in 12 patients with an initial ferritin of < 100 µg/L, are summarized below:

Changes in hemoglobin, ferritin, EPO dose, and Ferric Gluconate Dose for Patients with an Initial Ferritin of < 100 µg/L

	Pre hemoglobin (g/dl)	Post hemoglobin (g/dl)	Pre ferritin (µg/l)	Post ferritin (µg/l)	Pre erythropoietin (× 1000 i.u./wk)	Post erythropoietin (× 1000 i.u./wk)	Pre iron (ml/wk)	Post iron (ml/wk)
Median	10.05	11.00	68	210.5	9	6	10	2.5
Range	8.2–11.9	9.9–11.9	20–96	91–447	4–30	2–10	5–10	1.25–10
P		0.05		0.005		0.05		0.005

The mean hemoglobin increased from 10.1 g/dL to 11.0 g/dL. Mean EPO requirements decreased from 9000 U/week to 6000 U/week (Note that EPO doses were adjusted to maintain hemoglobin values in a prespecified range.) Mean Ferric Gluconate requirements decreased from 125 mg/week, to 31.25 mg/week.

No adverse events were reported in this study.

Pascual J, et. al., "Sodium ferric gluconate complex given intravenously for iron deficiency in hemodialysis," Clin Nephrol 1991 35 87

In a letter to the editor, Pascual J, et. al., reported the results of the administration of 1 gram of sodium ferric gluconate as 8 divided doses by slow i.v. injection to chronic hemodialysis patients. A total of 19 patients, of mean age 50 years, were stratified into the following 3 groups: **Group I** - 8 patients with iron deficiency anemia; **Group II** - 6 patients with anemia, iron deficiency, and concomitant treatment with nandrolone decanoate, and **Group III** - 5 patients with iron deficiency with a poor response to EPO. Results for hemoglobin (Hb) and serum ferritin (SF) values are shown below:

Group		Before i.v. iron	After i.v. iron***: 1 month	3 months	6 months
I	Hb (g/dl)*	7.7 ± 0.6	8.4 ± 0.9	8.9 ± 1.3	8.6 ± 1.3
	SF (µg/l)**	23 (14–48)	149 (67–263)	163 (107–561)	111 (98–329)
II	Hb (g/dl)*	8.4 ± 1.6	8.8 ± 0.8	9.3 ± 2.4	9.6 ± 1.3
	SF (µg/l)**	28 (17–37)	130 (45–452)	231 (174–370)	199 (151–392)
III	Hb (g/dl)*	8.5 ± 1.4	10.7 ± 2.5	11.2 ± 1.6	10.3 ± 2.7
	SF (µg/l)**	26 (20–39)	193 (58–1040)	213 (80–298)	154 (115–927)

* = Arithmetic mean ± SD, ** = Geometric means (range), *** = All values higher with respect to basal ones ($p < 0.05$, paired t-test)

Increases in hemoglobin were seen for all three groups, with the greatest increase in Group III patients. Serum ferritin increased in all groups up to 3 months, then declined. The authors concluded that "iron deficiency will become an increasing problem as erythropoietin is used more widely, unless prophylactic iron is administered i.v. when serum ferritin falls below adequate levels."

No adverse events were reported.

Pascual J, et. al., "Intravenous Fe-Gluconate-Na for Iron-Deficient Patients on Hemodialysis," Nephron 1992 60 121

In a letter to the editor, Pascual J, et. al. reported the results of a total of 59 hemodialysis patients with a baseline serum ferritin of < 50 ng/ml, treated with 1 gram of Ferrlecit, given as 8 divided doses. The results of the first 19 of these patients was described in a publication by Pascual J et. al. (discussed above).

Forty additional patients completed 6 months of follow-up: **Group I** - 18 patients with iron-deficiency anemia, **Group II** - 10 patients with iron-deficiency anemia and concomitant nandrolone decanoate therapy, and **Group III** - 12 patients with iron-deficiency anemia associated with erythropoietin therapy. The results are shown below:

	Group I	Group II	Group III
Sex (M/F)	9/9	7/3	6/6
Age, years	56±12	58±7	43±15
Time on HD, months	41±12	87±36	78±48
Hemoglobin, g/dl			
Basal	8.7±1.5	8.7±1.8	9.4±1.6
3 months*	10±1.6	10.8±2.7	11±1.4
6 months*	9.9±1.7	10.2±2	9.8±1.7
Serum ferritin, ng/ml			
Basal	27±1	29±1	27±1
1 month**	135±2	187±1	167±2
3 months**	143±2	163±2	199±2
6 months**	108±2	113±2	149±2
Positive responses	15/18	10/10	11/12

All values are expressed as arithmetic mean±SD except for serum ferritin (geometric mean±SD of log).
* $p<0.05$ with respect to controls (paired t test).
** $p<0.01$ with respect to basal values (paired t test).

Hemoglobin and serum ferritin increased in all groups up to 3 months, then began to decrease. The authors concluded that, "we obtained excellent repletion of iron stores and increased hemoglobin with (Ferrlecit) in our severely iron-deficient population."

Three patients experienced serious adverse events in this study, and are described below (Nephrol Dial Transplant 1992 7 271):

A 36 year-old male hemodialysis patient had a hemoglobin of 6.7 g/dL and serum ferritin of 53 ng/ml; he was given i.v. ferric gluconate (1 gram divided

into 8 post-hemodialysis doses). A few minutes after the first slow injection of 125 mg, he experienced malaise, heat, vomiting, and loin pain, lasting 5-6 minutes. No hypotension was noted. After the next dialysis session, another i.v. ferric gluconate infusion was attempted, but the adverse reaction reappeared and the treatment was withdrawn.

A 55 year-old female hemodialysis patient with a hemoglobin of 10.7 g/dL, and a serum ferritin of 12 ng/ml was started on i.v. ferric gluconate. After the first and second doses, the patient experienced intense epigastric pain lasting 3-4 hours, and no further doses were administered.

A 50 year-old woman on hemodialysis was receiving 80U/kg i.v. of EPO, and had a hemoglobin of 9.7 g/dL and serum ferritin of 22 ng/ml. Immediately following a slow infusion of 125 mg of ferric gluconate, an anaphylactoid reaction, characterized by severe hypotension, parasthesias of lips, fingers, and genitalia, without respiratory arrest, occurred. This reaction resolved after 1 hour.

Allegra V et. al., "Iron Deficiency in Maintenance Hemodialysis Patients: Assessment of Diagnosis Criteria and of Three Different Iron Treatments," Nephron 1991 57 175

In this study, the effect of 2 oral and 1 intravenous iron preparations, on hemoglobin, hematocrit, iron studies and red blood cell indices, were compared in maintenance hemodialysis patients.

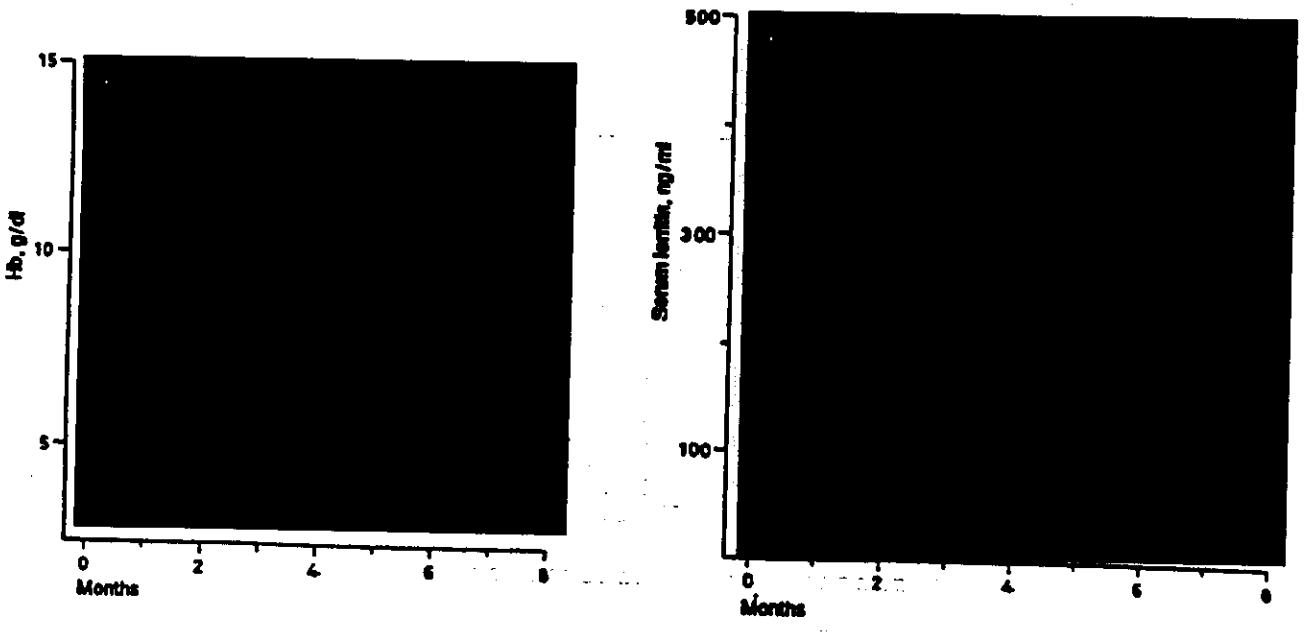
A total of 72 maintenance hemodialysis patients of mean age 51 years, on hemodialysis for a mean of 57 months, were studied. Patients underwent hemodialysis three times a week. Patients with chronic inflammatory diseases, hepatitis, bleeding, or patients taking androgens, were excluded from the study. No patients had received a blood transfusion for the previous 3 months.

Patients were divided into 3 groups, based on their baseline serum ferritin values: **Group A**; > 191 ng/ml, **Group B**; 19 to 191 ng/ml, and **Group C**; < 19 ng/ml. Each of these groups was further divided into **3 treatment subgroups**: 1) oral Fe-ferritin; 67.5 mg/day of Fe+3, 2) oral Fe-chondroitin sulfate; 60 mg/day of Fe+3, or 3) i.v. Fe-Gluconate Sodium; 31 mg of Fe+3 at the end of each dialysis session. Patients received iron for a total of 6 months. Follow-up was continued for 6 months after ending iron therapy.

The rate of "positive" hemoglobin responses at 6 months are shown in the table below. Note that a "positive" response was defined as an increase of ≥ 15% of the baseline value.

	Group A	Group B	Group C
Treatment 1	0/5(0%)	2/10(20%)	1/7(14%)
Treatment 2	0/5(0%)	1/6(17%)	3/7(43%)
Treatment 3	0/7(0%)	5/11(45%)	10/16(63%)

Note that for all iron preparations (Treatments 1 - 3), greater increases in hemoglobin were seen for patients with lower baseline serum ferritin values. The greatest increases were seen for i.v. Ferric Gluconate, compared to the two oral iron preparations. Hemoglobin and serum ferritin responses for patients who received i.v. Ferric Gluconate, AND had baseline serum ferritin values of < 191 ng/ml (i.e. Groups B and C of Treatment 3 patients) are shown below. Note that study medication was stopped after 6 months.



No adverse events were reported with the use of i.v. Ferric Gluconate in this study.

Summary of Published Reports

A summary of the published reports of the use of Ferrlecit to treat iron deficiency in chronic hemodialysis patients is shown below (Table 16, vol. 21, pp. 45-6).

Summary Table of Published Reports of the use of Ferrlecit in Chronic Hemodialysis Patients

Study	Patients treated with Fe-gluconate	Dose of Fe-gluconate	Hemoglobin (g/dL) Response	Serum Ferritin (SF) µg/L) Response
Navarro, et al.	27	375mg (62.5mg/month for 6 months)	Maintained at starting level (21) Baseline Mean: 10.7 6 month Mean: 10.6	Stable throughout study Baseline Mean: 187 6 month Mean: 196
Taylor, et al.	46	125mg/wk, 62.5 mg/wk, or 62.5 mg/fortnight for 6 months[3]	Pts w/ normal SF at Baseline BL: 9.05 6 mo: 11.25 Pts w/ low SF at Baseline BL: 10.05 6 mo: 11.00	Pts w/ normal SF at Baseline BL: 176 6 mo: 304.5 Pts w/ low SF at Baseline BL: 68 6 mo: 210.5
Pascual, et al.	40	1000mg (125mg @ 8 dialysis sessions)	I[3] BL: 8.7 6 mo: 9.9 II BL: 8.7 6 mo: 10.2 III BL: 9.4 6 mo: 9.8	I BL: 27 6 mo: 108 II BL: 29 6 mo: 113 III BL: 27 6 mo: 149
Pascual, et al.	19	1000mg (125mg @ 8 dialysis sessions)	I BL: 7.7 6 mo: 8.6 II BL: 8.4 6 mo: 9.6 III BL: 8.5 6 mo: 10.3	I BL: 23 6 mo: 111 II BL: 28 6 mo: 197 III BL: 26 6 mo: 154
Allegro, et al.	34[4]	31mg/dialytic session for 6 mo	15/34[5] responded (a15% increase from BL, including 5 who had not responded to oral iron; all had BL SF ≤ 191mg/L)	Initial rapid and significant increase, followed by slow decrease after end of therapy
	11	20mg/dialytic session for 6 mo	11/11 responded, all were iron deficient at baseline	Gradual increase until Hemoglobin stabilized, then rapid increase

1. Pts = Patients
2. Dosage was based on serum ferritin level and was adjusted throughout the treatment period.
3. BL = Baseline; mo = Month
4. These 34 pts were compared with 40 pts receiving oral iron supplements.
5. This rate of response was significantly higher than corresponding rate in pts receiving oral iron.

Note that, in addition to the favorable hemoglobin and serum ferritin responses, Ferrlecit was reported to decrease both the EPO dose, and maintenance intravenous iron requirements in the study by Taylor et. al.

Of the 177 renal dialysis patients exposed to Ferrlecit in the above studies, 3 experienced serious adverse events (Nephrol Dial Tranplant 1992 7 271): 1) malaise, heat, vomiting, and loin pain, which recurred on drug rechallenge and prohibited further drug use; 2) intense epigastric pain lasting 3-4 hours, which recurred on drug rechallenge, and prohibited further drug use, and; 3) an anaphylactoid reaction.

ATTACHMENT 10

APPEARS THIS WAY ON ORIGINAL

113 27 M	Abdominal pain Malaise	1150 mg
116 69 M	Transient hypotension Nausea and vomiting	1087.5 mg
118 73 F	Flush	1087.5 mg
127 64 F	Sweating	1025 mg
128 70 M	Flatulence	775 mg

Nissenson Study

Dr. Allen Nissenson treated 4 patients with a documented anaphylactic reaction to iron dextran, with Ferrlecit. One of these was patient #141 of study 5600-01, and was treated without incident. The characteristics and outcomes of the remaining four patients are shown below (vol. 22, p. 50). No adverse events were observed in these patients.

Adverse Events in Patients with a Previous Anaphylactic Reaction to Iron Dextran

	Patient Number			
Variable	102	101	104	105
Dextran Reaction	Anaphylaxis	Anaphylaxis	SOB, chest pain, hypotension	Anaphylaxis
Age	84	24	53	66
Gender	Male	Male	Female	Male
Etiology CRF	Diabetes	Glomerulonephritis	Alport's Syndrome	Diabetes
Total Ferrlecit	900 mg	1000 mg	900 mg	1000 mg
Administrations	8	9	8	9
Dates	10/3/96-12/12/96	9/16/96-11/20/96	10/21/96-12/24/96	10/21/96-12/24/96
AE	None	None	None	None

ATTACHMENT 11

APPEARS THIS WAY ON ORIGINAL

(11)

********** Entire Monograph **********

DESCRIPTION:

****
*
* WARNING *
* THE PARENTERAL USE OF COMPLEXES OF IRON AND *
* CARBOHYDRATES HAS RESULTED IN ANAPHYLACTIC- *
* TYPE REACTIONS. DEATHS ASSOCIATED WITH SUCH *
* ADMINISTRATION HAVE BEEN REPORTED. *
* THEREFORE, INFED SHOULD BE USED ONLY IN *
* THOSE PATIENTS IN WHOM THE INDICATIONS HAVE *
* BEEN CLEARLY ESTABLISHED AND LABORATORY *
* INVESTIGATIONS CONFIRM AN IRON DEFICIENT *
* STATE NOT AMENABLE TO ORAL IRON THERAPY. *
*
****

INFeD (iron dextran injection, USP) is a dark brown, slightly viscous sterile liquid complex of ferric hydroxide and dextran for intravenous or intramuscular use.
Each mL contains the equivalent of 50 mg of elemental iron (as an iron dextran complex), approximately 0.9% sodium chloride, in water for injection. Sodium hydroxide and/or hydrochloric acid may have been used to adjust pH. The pH of the solution is between 5.2 and 6.5.
The iron dextran complex has an average apparent molecular weight of 165,000.
apeutic Class: Hematinic

ACTIONS/CLINICAL PHARMACOLOGY:

GENERAL: After intramuscular injection, iron dextran is absorbed from the injection site into the capillaries and the lymphatic system. Circulating iron dextran is removed from the plasma by cells of the reticuloendothelial system, which split the complex into its components of iron and dextran. The iron is immediately bound to the available protein moieties to form hemosiderin or ferritin, the physiological forms of iron, or to a lesser extent to transferrin. This iron which is subject to physiological control replenishes hemoglobin and depleted iron stores.
Dextran, a polyglucose, is either metabolized or excreted. Negligible amounts of iron are lost via the urinary or alimentary pathways after administration of iron dextran.
The major portion of intramuscular injections of iron dextran is absorbed within 72 hours; most of the remaining iron is absorbed over the ensuing 3 to 4 weeks. Various studies involving intravenously administered 59Fe iron dextran to iron deficient subjects, some of whom had coexisting diseases, have yielded half-life values ranging from 5 hours to more than 20 hours. The 5-hour value was determined for 59Fe iron dextran from a study that used laboratory methods to separate the circulating 59Fe iron dextran from the transferrin-bound 59Fe. The 20-hour value reflects a half-life determined by measuring total 59Fe, both circulating and bound. It should be understood that these half-life values do not represent clearance of iron from the body. Iron is not easily eliminated from the body and accumulation of iron can be toxic.

INDICATIONS AND USAGE:

Intravenous or intramuscular injections of iron dextran are indicated for treatment of patients with documented iron deficiency in whom oral inistration is unsatisfactory or impossible.

CONTRAINDICATIONS:

Hypersensitivity to the product. All anemias not associated with iron deficiency.

WARNINGS:

WARNING
THE PARENTERAL USE OF COMPLEXES OF IRON AND CARBOHYDRATES HAS RESULTED IN ANAPHYLACTIC-TYPE REACTIONS. DEATHS ASSOCIATED WITH SUCH ADMINISTRATION HAVE BEEN REPORTED. THEREFORE, INFED SHOULD BE USED ONLY IN THOSE PATIENTS IN WHOM THE INDICATIONS HAVE BEEN CLEARLY ESTABLISHED AND LABORATORY INVESTIGATIONS CONFIRM AN IRON DEFICIENT STATE NOT AMENABLE TO ORAL IRON THERAPY.

A risk of carcinogenesis may attend the intramuscular injection of iron-carbohydrate complexes. Such complexes have been found under experimental conditions to produce sarcoma when large doses or small doses injected repeatedly at the same site were given to rats, mice, and rabbits, and possibly in hamsters.
The long latent period between the injection of a potential carcinogen and the appearance of a tumor makes it impossible to measure accurately the risk in man. There have, however, been several reports in the literature describing tumors at the injection site in humans who had previously received intramuscular injections of iron-carbohydrate complexes.
Large intravenous doses, such as used with total dose infusions (TDI), have been associated with an increased incidence of adverse effects. The adverse effects frequently are delayed (1-2 days) reactions typified by one or more of the following symptoms; arthralgia, backache, chills, dizziness, moderate to high fever, headache, malaise, myalgia, nausea, and vomiting. The onset is usually 8 hours after administration and symptoms generally subside within 3-4 days. These symptoms have also been reported following intramuscular injection and generally subside within 3-7 days. The etiology of these reactions is not known. The potential for a delayed reaction must be considered when estimating the risk/benefit of treatment.
The maximum daily dose should not exceed 2 mL undiluted iron dextran.
This preparation should be used with extreme care in patients with serious impairment of liver function.
It should not be used during the acute phase of infectious kidney disease.
Adverse reactions experienced following administration of INFeD may exacerbate cardiovascular complications in patients with pre-existing cardiovascular disease.

PRECAUTIONS:

GENERAL: Unwarranted therapy with parenteral iron will cause excess storage of iron with the consequent possibility of exogenous hemosiderosis. Such iron overload is particularly apt to occur in patients with hemoglobinopathies and other refractory anemias that might be erroneously diagnosed as iron deficiency anemias.
INFeD should be used with caution in individuals with histories of significant allergies and/or asthma.
Anaphylaxis and other hypersensitivity reactions have been reported after uneventful test doses as well as therapeutic doses of iron dextran injection. Therefore, administration of subsequent test doses during therapy should be considered. (See DOSAGE AND ADMINISTRATION: Administration.)
Epinephrine should be immediately available in the event of acute hypersensitivity reactions. (Usual adult dose: 0.5 mL of a 1+1000 solution, by subcutaneous or intramuscular injection.)
NOTE: Patients using beta-blocking agents may not respond adequately to epinephrine. Isoproterenol or similar beta-agonist agents may be required in these patients.
Patients with rheumatoid arthritis may have an acute exacerbation of joint pain and swelling following the administration of INFeD.
Reports in the literature from countries outside the United States (in

particular, New Zealand) have suggested that the use of intramuscular iron dextran in neonates has been associated with an increased incidence of gram-negative sepsis, primarily due to E. Coli.

INFORMATION FOR PATIENTS: Patients should be advised of the potential adverse reactions associated with the use of INFeD.

DRUG/LABORATORY TEST INTERACTIONS: Large doses of iron dextran (5 mL or more) have been reported to give a brown color to serum from a blood sample drawn 4 hours after administration.

The drug may cause falsely elevated values of serum bilirubin and falsely decreased values of serum calcium.

Serum iron determinations (especially by colorimetric assays) may not be meaningful for 3 weeks following the administration of iron dextran.

Serum ferritin peaks approximately 7 to 9 days after an intravenous dose of INFeD and slowly returns to baseline after about 3 weeks.

Examination of the bone marrow for iron stores may not be meaningful for prolonged periods following iron dextran therapy because residual iron dextran may remain in the reticuloendothelial cells.

Bone scans involving 99m Tc-diphosphonate have been reported to show a dense, crescentic area of activity in the buttocks, following the contour of the iliac crest, 1 to 6 days after intramuscular injections of iron dextran.

Bone scans with 99m Tc-labeled bone seeking agents, in the presence of high serum ferritin levels or following iron dextran infusions, have been reported to show reduction of bony uptake, marked renal activity, and excessive blood pool and soft tissue accumulation.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: See WARNINGS.

PREGNANCY: Pregnancy Category C: Iron dextran has been shown to be teratogenic and embryocidal in mice, rats, rabbits, dogs, and monkeys when given in doses of about 3 times the maximum human dose.

No consistent adverse fetal effects were observed in mice, rats, rabbits, dogs and monkeys at doses of 50 mg iron/kg or less. Fetal and maternal toxicity has been reported in monkeys at a total intravenous dose of 90 mg iron/kg over a 14 day period. Similar effects were observed in mice and rats on administration of a single dose of 125 mg iron/kg. Fetal abnormalities in rats and dogs were observed at doses of 250 mg iron/kg and higher. The animals used in these tests were not iron deficient. There are no adequate and well- controlled studies in pregnant women. INFeD should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

PLACENTAL TRANSFER: Various animal studies and studies in pregnant humans have demonstrated inconclusive results with respect to the placental transfer of iron dextran as iron dextran. It appears that some iron does reach the fetus, but the form in which it crosses the placenta is not clear.

NURSING MOTHERS: Caution should be exercised when INFeD is administered to a nursing woman. Traces of unmetabolized iron dextran are excreted in human milk.

PEDIATRIC USE: Not recommended for use in infants under 4 months of age (See DOSAGE AND ADMINISTRATION.).

SEE PRECAUTIONS

DRUG INTERACTIONS:

ADVERSE REACTIONS:

SEVERE/FATAL: Anaphylactic reactions have been reported with the use of iron dextran injection; on occasions these reactions have been fatal. Such reactions, which occur most often within the first several minutes of administration, have been generally characterized by sudden onset of respiratory difficulty and/or cardiovascular collapse. (See boxed WARNING and PRECAUTIONS: General, pertaining to immediate availability of epinephrine.)

CARDIOVASCULAR: Chest pain, chest tightness, shock, hypotension, hypertension, tachycardia, flushing, arrhythmias. (Flushing and hypotension may occur from too rapid injections by the intravenous route.)

DERMATOLOGIC: Urticaria, pruritus, purpura, rash.

GASTROINTESTINAL: Abdominal pain, nausea, vomiting, diarrhea.

HEMATOLOGIC/LYMPHATIC: Leucocytosis, lymphadenopathy.

MUSCULOSKELETAL/SOFT TISSUE: Arthralgia, arthritis (may represent reactivation in patients with quiescent rheumatoid arthritis--See PRECAUTIONS: General), myalgia; backache; sterile abscess, atrophy/fibrosis (intramuscular injection site); brown skin and/or underlying tissue discoloration (staining), soreness or

pain at or near intramuscular injection sites; cellulitis; swelling; inflammation; local phlebitis at or near intravenous injection site.
NEUROLOGIC: Convulsions, seizures, syncope, headache, weakness, unresponsiveness, paresthesia, febrile episodes, chills, dizziness, disorientation, numbness.
RESPIRATORY: Respiratory arrest, dyspnea, bronchospasm.
UROLOGIC: Hematuria.
DELAYED REACTIONS: Arthralgia, backache, chills, dizziness, fever, headache, malaise, myalgia, nausea, vomiting (See WARNINGS.).
MISCELLANEOUS: Febrile episodes, sweating, shivering, chills, malaise, altered taste.

OVERDOSAGE:

Overdosage with iron dextran is unlikely to be associated with any acute manifestations. Dosages of iron dextran in excess of the requirements for restoration of hemoglobin and replenishment of iron stores may lead to hemosiderosis. Periodic monitoring of serum ferritin levels may be helpful in recognizing a deleterious progressive accumulation of iron resulting from impaired uptake of iron from the reticuloendothelial system in concurrent medical conditions such as chronic renal failure, Hodgkin's disease, and rheumatoid arthritis. The LD50 of iron dextran is not less than 500 mg/kg in the mouse.

DOSAGE AND ADMINISTRATION:

Oral iron should be discontinued prior to administration of INFeD.
DOSAGE:
I. IRON DEFICIENCY ANEMIA: Periodic hematologic determination (hemoglobin and hematocrit) is a simple and accurate technique for monitoring hematological response, and should be used as a guide in therapy. It should be recognized that iron storage may lag behind the appearance of normal blood morphology. Serum iron, total iron binding capacity (TIBC) and percent saturation of transferrin are other important tests for detecting and monitoring the iron deficient state. After administration of iron dextran complex, evidence of a therapeutic response may be seen in a few days as an increase in the reticulocyte count. Although serum ferritin is usually a good guide to body iron stores, the correlation of body iron stores and serum ferritin may not be valid in patients on chronic renal dialysis who are also receiving iron dextran complex. Although there are significant variations in body build and weight distribution among males and females, the accompanying table and formula represent a convenient means for estimating the total iron required. This total iron requirement reflects the amount of iron needed to restore hemoglobin concentration to normal or near normal levels plus an additional allowance to provide adequate replenishment of iron stores in most individuals with moderately or severely reduced levels of hemoglobin. It should be remembered that iron deficiency anemia will not appear until essentially all iron stores have been depleted. Therapy, thus, should aim at not only replenishment of hemoglobin iron but iron stores as well.
Factors contributing to the formula are shown below.

$$\frac{\text{mg blood iron}}{\text{lb body weight}} = \frac{\text{mL blood}}{\text{lb body weight}} \times \frac{\text{g hemoglobin}}{\text{mL blood}} \times \frac{\text{mg iron}}{\text{g hemoglobin}}$$

a) Blood volume..... 65 mL/kg body weight
b) Normal hemoglobin (males and females)
over 15 kg (33 lbs)..... 14.8 g/dl
15 kg (33 lbs) or less..... 12.0 g/dl
c) Iron content of hemoglobin. 0.34%
d) Hemoglobin deficit
e) Weight

Based on the above factors, individuals with normal hemoglobin levels will require approximately 33 mg of blood iron per kilogram of body weight (15 mg/lb).
NOTE: The table and accompanying formula are applicable for dosage determinations only in patients with iron deficiency anemia; they are not to be used for dosage determinations in patients requiring iron replacement for

blood loss.

TOTAL INFED(R) REQUIREMENT FOR HEMOGLOBIN RESTORATION AND IRON STORES REPLACEMENT*

PATIENT LEAN BODY WEIGHT		MILLILITER REQUIREMENT OF INFED BASED ON OBSERVED HEMOGLOBIN OF							
KG	LB	3 (g/dl)	4 (g/dl)	5 (g/dl)	6 (g/dl)	7 (g/dl)	8 (g/dl)	9 (g/dl)	10 (g/dl)
5	11	3	3	3	3	2	2	2	2
10	22	7	6	6	5	5	4	4	3
15	33	10	9	9	8	7	7	6	5
20	44	16	15	14	13	12	11	10	9
25	55	20	18	17	16	15	14	13	12
30	66	23	22	21	19	18	17	15	14
35	77	27	26	24	23	21	20	18	17
40	88	31	29	28	26	24	22	21	19
45	99	35	33	31	29	27	25	23	21
50	110	39	37	35	32	30	28	26	24
55	121	43	41	38	36	33	31	28	26
60	132	47	44	42	39	36	34	31	28
65	143	51	48	45	42	39	36	34	31
70	154	55	52	49	45	42	39	36	33
75	165	59	55	52	49	45	42	39	35
80	176	63	59	55	52	48	45	41	38
85	187	66	63	59	55	51	48	44	40
90	198	70	66	62	58	54	50	46	42
95	209	74	70	66	62	57	53	49	45
100	220	78	74	69	65	60	56	52	47
105	231	82	77	73	68	63	59	54	50
110	242	86	81	76	71	67	62	57	52
115	253	90	85	80	75	70	64	59	54
120	264	94	88	83	78	73	67	62	57

* Table values were calculated based on a normal adult hemoglobin of 14.8 g/dl for weights greater than 15 kg (33 lbs) and a hemoglobin of 12.0 g/dl for weights less than or equal to 15 kg (33 lbs).

The total amount of INFeD in mL required to treat the anemia and replenish iron stores may be approximated as follows:

ADULTS AND CHILDREN OVER 15 KG (33 LBS): See Dosage Table.

Alternatively the total dose may be calculated:

Dose (mL) = 0.0442 (Desired Hb-Observed Hb) X LBW +(0.26 X LBW)

Based on: Desired Hb = the target Hb in g/dl.

Observed Hb = the patient's current hemoglobin in g/dl.

LBW = Lean body weight in kg. A patient's lean body weight (or actual body weight if less than lean body weight) should be utilized when determining dosage.

For males: LBW = 50 kg + 2.3 kg for each inch of patient's height over 5 feet

For females: LBW = 45.5 kg + 2.3 kg for each inch of patient's height over 5 feet

To calculate a patient's weight in kg when lbs are known:

$$\frac{\text{patient's weight in pounds}}{2.2} = \text{weight in kilograms}$$

CHILDREN 5-15 KG (11-33 LBS): See Dosage Table.

INFeD should not normally be given in the first four months of life. (See PRECAUTIONS: Pediatric Use.)

Alternatively the total dose may be calculated:

Dose (mL) = 0.0442 (Desired Hb-Observed Hb) X W +(0.26 X W)

Based on: Desired Hb = the target Hb in g/dl. (Normal Hb for Children 15 kg or

less is 12 g/dl.)
W = Weight in kg.
calculate a patient's weight in kg when lbs are known:

$$\frac{\text{patient's weight in pounds}}{2.2} = \text{weight in kilograms}$$

II. IRON REPLACEMENT FOR BLOOD LOSS: Some individuals sustain blood losses on an intermittent or repetitive basis. Such blood losses may occur periodically in patients with hemorrhagic diatheses (familial telangiectasia; hemophilia; gastrointestinal bleeding) and on a repetitive basis from procedures such as renal hemodialysis.
Iron therapy in these patients should be directed toward replacement of the equivalent amount of iron represented in the blood loss. The table and formula described under I. IRON DEFICIENCY ANEMIA are NOT applicable for simple iron replacement values.
Quantitative estimates of the individual's periodic blood loss and hematocrit during the bleeding episode provide a convenient method for the calculation of the required iron dose.
The formula shown below is based on the approximation that 1 mL of normocytic, normochromic red cells contains 1 mg of elemental iron:

Replacement iron (in mg) = Blood loss (in mL) x hematocrit
Example: Blood loss of 500 mL with 20% hematocrit
Replacement Iron = 500 x 0.20 = 100 mg
INFeD dose=$\frac{100 \text{ mg}}{50}$=2 mL

ADMINISTRATION: The total amount of INFeD required for the treatment of iron deficiency anemia or iron replacement for blood loss is determined from the table or appropriate formula. (See Dosage.)
1 INTRAVENOUS INJECTION--PRIOR TO RECEIVING THEIR FIRST INFeD THERAPEUTIC DOSE, PATIENTS SHOULD BE GIVEN AN INTRAVENOUS TEST DOSE OF 0.5 mL. (See CAUTIONS: General.) THE TEST DOSE SHOULD BE ADMINISTERED AT A GRADUAL RATE OVER AT LEAST 30 SECONDS. Although anaphylactic reactions known to occur following INFeD administration are usually evident within a few minutes, or sooner, it is recommended that a period of an hour or longer elapse before the remainder of the initial therapeutic dose is given.
Individual doses of 2 mL or less may be given on a daily basis until the calculated total amount required has been reached. INFeD is given undiluted at a SLOW GRADUAL RATE not to exceed 50mg (1 mL) per minute.
2. INTRAMUSCULAR INJECTION--PRIOR TO RECEIVING THEIR FIRST INFeD THERAPEUTIC DOSE, ALL PATIENTS SHOULD BE GIVEN AN INTRAMUSCULAR TEST DOSE OF 0.5mL. (See PRECAUTIONS: General.) The test dose should be administered in the same recommended test site and by the same technique as described in the last paragraph of this section. Although anaphylactic reactions known to occur following INFeD administration are usually evident within a few minutes or sooner, it is recommended that at least an hour or longer elapse before the remainder of the initial therapeutic dose is given.
If no adverse reactions are observed, INFeD can be given according to the following schedule until the calculated total amount required has been reached. Each day's dose should ordinarily not exceed 0.5 mL (25 mg of iron) for infants under 5 kg (11 lbs); 1.0 mL (50 mg of iron) for children under 10 kg (22 lbs); and 2.0 mL (100 mg of iron) for other patients.
INFeD should be injected only into the muscle mass of the upper outer quadrant of the buttock- -never into the arm or other exposed areas--and should be injected deeply, with a 2-inch or 3-inch 19 or 20 gauge needle. If the patient is standing, he/she should be bearing his/her weight on the leg opposite the injection site, or if in bed, he/she should be in the lateral position with injection site uppermost. To avoid injection or leakage into the subcutaneous tissue, a Z- track technique (displacement of the skin laterally prior to injection) is recommended.
Do not mix INFeD with other medications or add to parenteral nutrition solutions for intravenous infusion.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever the solution and container

ATTACHMENT 12

APPEARS THIS WAY ON ORIGINAL

9.2 ADVERSE EVENTS

9.2.1 BRIEF SUMMARY OF ADVERSE EVENTS

Eighteen patients were hospitalized during the study; 1 of these died. None of the serious AEs were considered by the investigator to be related to study drug.

Adverse events are summarized in Table 16. The majority of patients (93.8%) experienced at least 1 AE; by treatment group the incidences of AEs were 92.7% of patients in the low-dose group, 95.7% in high-dose group, and 92.0% in the historical (oral-dose) control group (Table 16). The body systems in which the majority of AEs occurred were body as a whole (experienced by 61.9% of patients), cardiovascular disorders (56.6%), gastrointestinal disorders (42.5%), and central and peripheral nervous systems (41.6%).

The most frequent AEs experienced by patients in all 3 treatment groups were hypotension (48.7% of patients), nausea (31.9%), and vomiting (22.1%). All of these symptoms, as well as cramps, are commonly associated with hemodialysis (54). Cramps and/or leg cramps (central and peripheral nervous system) were experienced by 35 (40.0%) of the dose-control groups and by none of the historical (oral-dose) control patient; however, muscle cramps (autonomic nervous system) were experienced by 17 (68.0%) of the historical (oral-dose) control patients but by none of the dose treatment patients. Because the dose-control investigator categorized cramps as central and peripheral nervous system events, while cramps for the historical (oral-dose) control patients were categorized as autonomic nervous system events, we combined all categories of cramps and compared the 3 treatment groups. Results are in Table 16a; the proportion of patients receiving Ferrlecit who experienced cramps was lower than the corresponding proportion of control patients.

Thirty-two of 88 patients in the Ferrlecit dose groups experienced a reaction at the injection site. None of these reactions were considered by the investigator to be related to the study drug. Pain at the site of vascular access is a common hemodialysis symptom. Injection site reaction was not recorded for patients in the historical (oral-dose) control group.

Most events were considered by the investigator to be mild or moderate in intensity and most were not related to Ferrlecit (Appendix 13.2.3). Adverse events that were possibly or probably related to Ferrlecit were experienced by 9 patients (#'s 102, 112, 116, 117, 121, 302, 311, 333, 335). These adverse events and the number of times they were reported were nausea (4), vomiting (3), rash (2), and abdominal pain, back pain, fatigue, syncope, cramps, agitation, menorrhagia, pruritus, chest pain, paresthesia, and abnormal erythrocytes (1 each).

9.2.2 DISPLAY OF ADVERSE EVENTS

Adverse events are summarized by body system in Table 16.

Table 16. Summary of Adverse Events by Body System

Body System Adverse Event	Treatment Group 500 mg (N = 41) n %	 1000 mg (N = 47) n %	 Control* (N = 25) n %	Total (N = 113) n %	p-value+ 500 vs. 1000
ANY BODY SYSTEM	38 (92.7)	45 (95.7)	23 (92.0)	106 (93.8)	0.661
BODY AS A WHOLE					
INJECTION SITE REACTION	27 (65.9)	34 (72.3)	9 (36.0)	70 (61.9)	0.644
CHEST PAIN	15 (36.6)	17 (36.2)	-	32 (28.3)	1.000
HEADACHE	1 (2.4)	8 (17.0)	9 (36.0)	18 (15.9)	0.033
PAIN	2 (4.9)	7 (14.9)	6 (24.0)	15 (13.3)	0.166
FATIGUE	5 (12.2)	6 (12.8)	-	11 (9.7)	1.000
FEVER	3 (7.3)	4 (8.5)	-	7 (6.2)	1.000
ASTHENIA	2 (4.9)	2 (4.3)	2 (8.0)	6 (5.3)	1.000
PAIN BACK	1 (2.4)	5 (10.6)	-	6 (5.3)	0.209
ABDOMINAL PAIN	0 (0.0)	3 (6.4)	3 (12.0)	6 (5.3)	0.245
MALAISE	1 (2.4)	4 (8.5)	-	5 (4.4)	0.366
RIGORS	3 (7.3)	1 (2.1)	-	4 (3.5)	0.335
CHILLS	1 (2.4)	2 (4.3)	-	3 (2.7)	1.000
PAIN ARM	0 (0.0)	0 (0.0)	2 (8.0)	2 (1.8)	
INFECTION	0 (0.0)	2 (4.3)	-	2 (1.8)	0.497
ABORTION	1 (2.4)	1 (2.1)	-	2 (1.8)	1.000
PAIN LEGS	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
INFLUENZA-LIKE SYMPTOMS	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
INFLAMMATORY REACTION	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
ABDOMEN ENLARGED	1 (2.4)	0 (0.0)	-	1 (0.9)	0.466
HERNIA	0 (0.0)	1 (2.1)	-	1 (0.9)	1.000
CARDIOVASCULAR DISORDERS	18 (43.9)	23 (48.9)	23 (92.0)	64 (56.6)	0.673
HYPOTENSION	14 (34.1)	18 (38.3)	23 (92.0)	55 (48.7)	0.825
HYPERTENSION	7 (17.1)	10 (21.3)	-	17 (15.0)	0.788

(continued)

* Historical control data taken from Abuelo et al. (54).
\+ p-value is associated with Fisher's Exact Test.
\# - = Data not reported.

(Cross-reference: Appendix 13.2.3)